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ORIGINAL ARTICLE

Diagnostic Potential of Interleukin-40 and Interleukin-41 in Diabetic Kidney Disease

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ABSTRACT

Background: *Diabetic kidney disease (DKD) is a significant microvascular consequence of diabetes mellitus and a predominant cause of end-stage renal disease (ESRD) globally. Recent studies have emphasized the significance of inflammatory mediators in the etiology and prognosis of diabetic kidney disease (DKD). However, the impact of certain cytokines, such as Interleukin-40 (IL-40) and Interleukin-41 (IL-41),has not been adequately elucidated with limited published data.* ***Objectives:*** *This study aimed to demonstrate the diagnostic potential of IL-40 and IL-41 in individuals with diabetic kidney disease (DKD).* ***Methodology:*** *This case-control study enrolled 84 participants (42 DKD patients and 42 healthy controls). The serum levels of IL-40 and IL-41 were measured using ELISA. Statistical analysis was performed using SPSS, and the diagnostic value of IL-40 and IL-41 was evaluated using receiver operating characteristic (ROC) curve analysis.* ***Results:*** *The investigation demonstrated a markable decrease in IL-40 and IL-41 concentrations in patients with diabetic kidney disease (DKD) compared to healthy controls (IL-40: 15.791 ± 8.012 pg/mL vs. 29.859 ± 8.742 pg/mL, p = 0.0002; IL-41: 0.525 ± 0.649 pg/mL vs. 3.013 ± 0.983 pg/mL, p = 0.0004). Moreover, the ROC curve analysis indicated that IL-41 exhibited greater diagnostic accuracy (AUC = 98.394%) than IL-40 (AUC = 89.646%), with elevated sensitivity (95.238%) and specificity (95.349%).* ***Conclusion:*** *The marked decrease in IL-40 and IL-41 levels in patients with DKD indicates their possible function as immunological indicators of disease progression. Assessing IL-40 and IL-41 concentrations, in conjunction with additional inflammatory markers, may enhance early identification and management of diabetic kidney disease (DKD).*

INTRODUCTION

Diabetic kidney disease (DKD) is a prevalent, difficult, and burdensome long-term complication of diabetes, representing approximately 40% of global end-stage kidney disease (ESKD) cases, and is a significant vascular complication of diabetes mellitus. It affects approximate 30–50% of individuals with type 1 diabetes (T1DM) and 20–40% of those with type 2 diabetes (T2DM), and originates from glomerular hyperfiltration caused by hyperglycemia-induced modifications in the tubuloglomerular feedback mechanism, along with direct cellular injury resulting from glucotoxicity. DKD is characterized by persistent albuminuria, declining glomerular filtration rate (GFR), and systemic consequences.[1,2,3,4]

DKD demonstrates deleterious structural alterations, including enlargement of the glomerular basement membrane, podocyte depletion, thickening of the mesangial matrix, and fusion of foot processes [5]. The pathophysiology of diabetic kidney disease (DKD) is multifaceted, encompassing hyperglycemia-induced renal hemodynamic alterations, oxidative stress, inflammatory responses, hypoxia, and activation of the renin-angiotensin-aldosterone system (RAAS). Furthermore, genetic, epigenetic, and immunological variables significantly influence disease progression.[6,7,8] Recent studies have emphasized the importance of the immune system and inflammatory mediators in the etiology of DKD, indicating that cytokines may be pivotal in disease progression[9].

Interleukin-40 (IL-40) and Interleukin-41 (IL-41) have been identified as possible modulators of immunological responses. IL-40 has been associated with B-cell-mediated immune responses, but IL-41 has demonstrated anti-inflammatory effects in multiple disease models. Nonetheless, their precise functions in renal inflammation and fibrosis in diabetes remain predominantly unexamined. [10,11,6].

In addition, few data for these two cytokines clarifying their role in DKD, are present in Iraq This study aimed to assess the concentrations of IL-40 and IL-41 in patients with diabetic kidney disease (DKD) relative to healthy controls and to investigate their potential as diagnostic biomarkers for these conditions. We aimed to enhance the understanding of the inflammatory processes implicated in DKD and to identify novel targets for therapeutic intervention.

METHODOLOGY

Study Design and Population

This case-control study included 84 participants (42 per group), and was categorized as follows: 42 in the d iabetic kidney disease group (DKD). The diagnosis of DKD was confirmed by estimated glomerular filtration rate (eGFR), where normal' eGFR is defined as 90 ml/min/1.73m² or more, caution should be applied as follows: an eGFR of 60 to 89 ml/min/1.73m² should be classified as normal in the absence of any other evidence of CKD.e GFR was calculated on line using CKD-EPI equation which depends on serum creatinine level(mg/dl), age in year, black race or not and gender. , history of diabetes, HbA1c, and serum albumin level . the healthy control group included 42 participants with no history of diabetes, hypertension, or renal disorders. Normal fasting blood glucose (< 100 mg/dL) and HbA1c levels (< 5.7%). The Healthy control group was comprised of 42 participants. These study was conducted at Al-Hussein Medical City Teaching Hospital between November 2024 and January 2025. Demographic data (age, sex, and weight) and clinical data (disease duration, and medications) were recorded using standardized questionnaires.

Inclusion and Exclusion Criteria

Exclusion criteria for the patients group were: chronic liver disease, acute infections and inflammation, pregnancy, other autoimmune diseases and use of nephrotoxic medications.

Sample Collection

Venous blood samples (5 mL) were collected using BD Vacutainer® serum tubes (model: 20231202; Becton Dickinson, USA). Serum was separated by centrifugation (2,000-3,000 RBM, 20 min, room temperature) and stored at -80°C until analysis (within storage: 6 months).

Immunological Assay of IL40 and IL41

Serum levels of IL-40 and IL-41 were measured using commercially available ELISA kits (BT LAB, China; Cat. No. E4654Hu for IL-40 and Cat. No. E3491Hu for IL-41), according to the manufacturer's instructions. Briefly, 100 µL of each standard or sample was added to wells pre-coated with antibodies specific to human IL-40 or IL-41, followed by incubation and washing to remove unbound substances. Enzyme-linked secondary antibodies were added, and the colorimetric reaction was developed using TMB substrate. Absorbance was measured at 450 nm, and concentrations were calculated from a standard curve generated with known concentrations of each target protein.

Biochemical Parameters Assessment

Ferritin levels were determined using a chemiluminescent microparticle immunoassay (CMIA), which measures the antigen-antibody reaction through luminescence intensity proportional to ferritin concentration[29]. Serum iron and total iron-binding capacity (TIBC) were measured using colorimetric methods based on the formation of a colored complex with ferrozin. Serum phosphorus was assessed using the molybdate UV method, where inorganic phosphorus reacts with ammonium molybdate to form a phosphomolybdate complex measured at 340 nm.

Statistical analysis

Statistical analysis was performed by (SPSS , Version 21). Data are expressed as mean ± SD. Unpaired Student's *t*-test was performed for comparisons. Receiver operating characteristic (ROC) curves were plotted and the cut-off value, area under curve (AUC), sensitivity (%), specificity (%), positive predictive value (NPV), negative predictive value % (NPV), and accuracy were determined Statistical. Significance was set at $P < 0.05$.

Ethical approval

The Ethical Committees of the Kerbela Health Directorate approved the study with reference number 3773 at 3-11-2024. Written informed consent was obtained from all participants prior to enrollment. The study adhered to the ethical principles outlined in the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Data confidentiality was maintained using anonymized identifiers.

RESULTS

The study revealed a significant reduction in IL-40 and IL-41 levels in patientse with DKD compared with healthy controls. Specifically, IL-40 levels were (15.791 ± 8.012 pg/mL) in DKD patients versus (29.859 ± 8.742 pg/mL) in controls ($p = 0.0002$). Similarly, IL-41 levels were markedly lower in patients with DKD (0.525 ± 0.649 pg/mL) than in controls (3.013 ± 0.983 pg/mL, $p = 0.0004$) (Table 1 and figure 1).

Serum ferritin levels were significantly elevated in patients with DKD (315.586 ± 215.687 ng/mL) compared to controls (78.209 ± 29.323 ng/mL, $p = 0.0006$). Phosphorus levels were also higher in patients with DKD (5.055 ± 1.379 mg/dL) tnan in controls (3.228 ± 0.474 mg/dL, $p = 0.0003$). Additionally, eGFR was significantly lower in patients with DKD (8.888 ± 2.699 mL/min/1.73m²) than in controls (132.226 ± 8.288 mL/min/1.73m², $p = 0.0002$). The study observed a significant decrease in serum iron levels in patients with DKD (82.833 ± 50.662 µg/dL) compared to controls (104.349 ± 14.832 µg/dL, $p = 0.011$). In contrast, no significant difference was observed in UIBC levels between patients with DKD and controls (247.781 ± 81.081 µg/dL vs. 228.163 ± 34.868 µg/dL, $p = 0.155$) (Table 1, figure 1and 2).

Table 1: Serum level of IL40 , IL41 , ferritin Iron ,unsaturated iron binding capacity, phosphorus and eGFR for patients and controls[a]

Parameters	Control Group		DKD Group		p. value
	Mean	Std. Deviation	Mean	Std. Deviation	
IL-40 (ng/mL)	29.859	8.742	15.791	8.012	**0.0004**
IL-41 (ng/mL)	3.013	0.983	0.525	0.649	**0.0004**
S.ferritin (ng/mL)	78.209	29.323	315.586	115.687	**0.0006**
UIBC (µg/dL)	228.163	34.868	247.781	81.081	**0.155**
Iron (µg/dL)	104.349	14.832	82.833	50.662	**0.011**
Serum phosphorus (mg/dL)	3.228	0.474	5.055	1.379	**0.0003**
eGFR (ml/min/1.73m²)	132.226	8.288	8.888	2.699	**0.0002**

a:DKD,=diabetic kidney disease. IL-40 = Interleukin-40. IL-41= Interleukin-41.UIBC= Unsaturated iron- binding capacity. eGFR= estimated glomerular filtration rate.

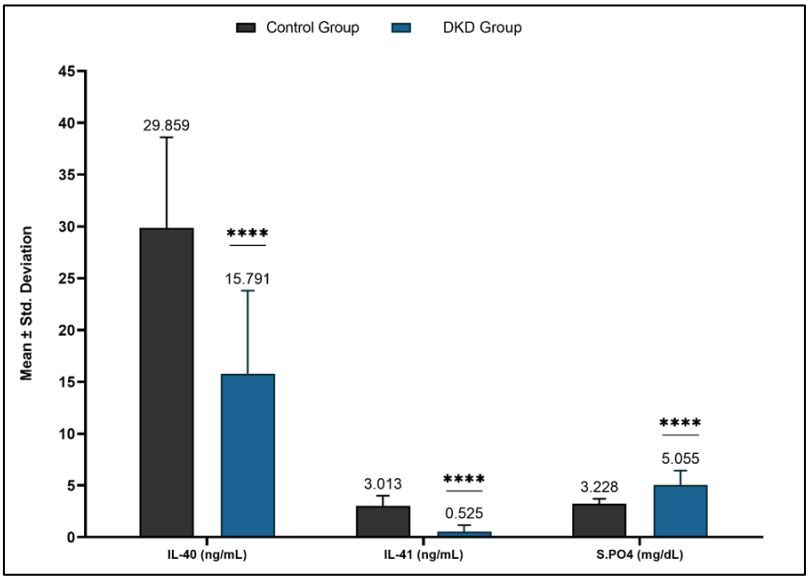

Figure 1. Interleukin 40, 41 & Serum phosphorus for study groups

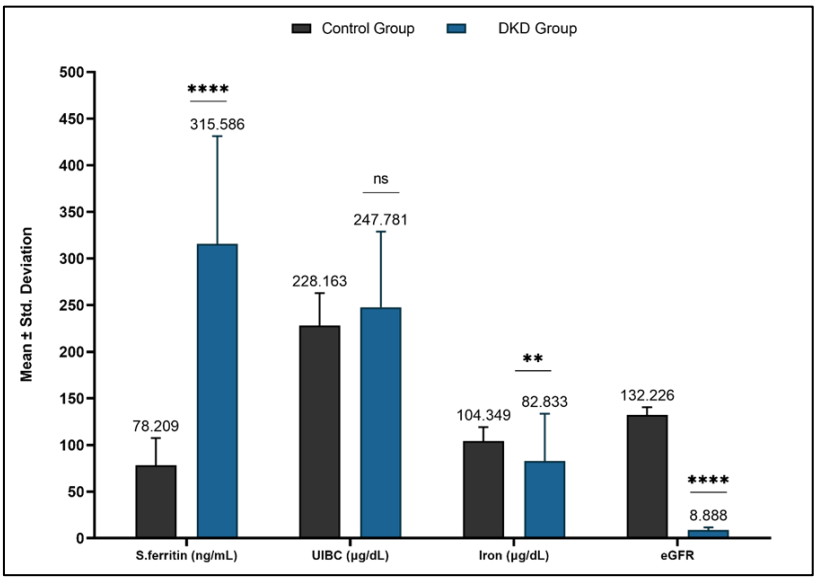

Figure 2. Inflammatory Markers & eGFR (ml/min/1.73m²) for the Study Outcomes

ROC curve analysis demonstrated that IL-41 had superior diagnostic accuracy (AUC = 98.394%) than to IL-40 (AUC = 89.646%). IL-41 exhibited higher sensitivity (95.238%) and specificity (95.349%) in distinguishing patients with DKD from healthy controls (Table 2 and Figure 3).

Table 2. Diagnostic Value of IL-40 and IL-41 in Distinguishing Study

Groups			
Metrics		**DKD vs Control**	
		IL-40	**IL-41**
Std. Error		0.039	0.011
Asymptotic Sig.		0.003	0.001
Asymptotic 95% Confidence Interval	Lower Bound	0.820	0.963
	Upper Bound	0.973	1.000
Cutoff Point		17.960	1.850
Sensitivity		83.333%	95.238%
Specificity		97.674%	95.349%
Accuracy		90.588%	95.294%
Positive Predictive Value		97.222%	95.238%
Negative Predictive Value		85.714%	95.349%

a: Statically significant at p- value <= 0.01

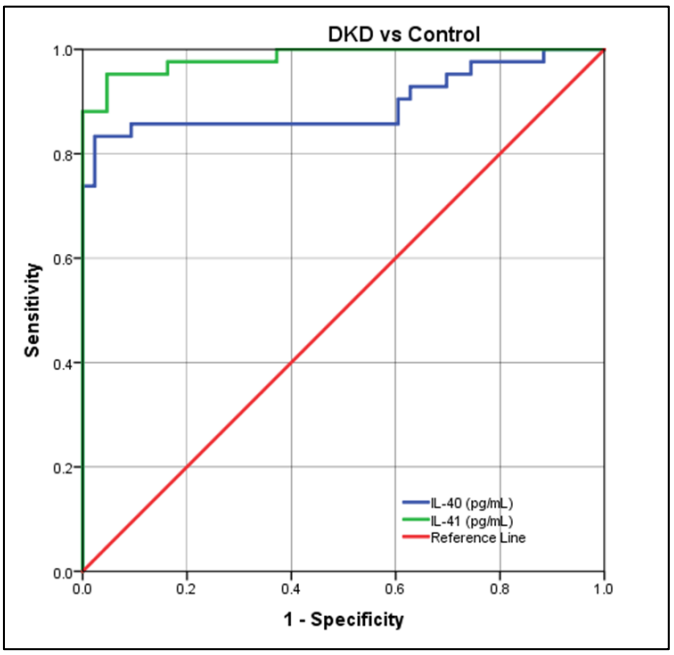

Fig. 3: Diagnostic Performance of IL-40 and IL-41 in Distinguishing Study Groups

DISCUSSION

Thise study revealed a markable decrease in IL-40 and IL-41 levels in patients with diabetic kidney disease (DKD) relative to healthy controls. thise data indicates possible dysregulation of these cytokines in the inflammatory response linked to DKD. Although IL-40 has been associated with B-cell-mediated immune responses, its function in chronic renal disorders is still poorly understood. Likewise, IL-41, which is recognized for its anti-inflammatory characteristics, may provide a protective function in the initial phases of DKD; however, its decline in later stages could signify an exhausted immune response. Our findings suggest a diminished regulatory function of these molecules in moderating the inflammatory response.

The observed reduction in IL-40 and IL-41 levels may augment the activity of pro-inflammatory cytokines, including IL-6 and TNF-α, which are established factors in the deterioration of renal function in diabetic kidney disease (DKD)[12],[30] .This study highlights the necessity for additional research to clarify the mechanisms connecting IL-40 and IL-41 to inflammatory pathways in renal disorders, which may aid in the formulation of innovative therapeutic methods in the future. There was a notable elevation in serum .ferritin levels in patients with DKD (315.586 ± 215.687 ng/mL) compared to those in the control group (78.209 ± 29.323 ng/mL, p = 0.0006).

Ferritin is acknowledged as an inflammatory marker that signifies oxidative stress and chronic inflammation, both of which are pivotal in the progression of diabetic kidney disease (DKD)[13] Moreover, Ferritin levels may be elevated in chronic renal disease due to declining kidney function or inflammation caused by diabetes. This inflammatory condition is thought to hinder erythropoietin (EPO) production and diminish the physiological response to it, thereby worsening anemia in this patient demographic [14] The findings of UIBC indicated No statistically significant differences were detected between the two groups.

The mean value in the DKD group was 247.781± 81.081, whereas that in the control group was 228.163 ± 34.868 (p=0.155). This discovery indicates modifications in iron metabolism potentially linked to chronic inflammatory responses in diabetic kidney disease (DKD)[15]. A reduction in UIBC indicateds a decline in transferrin concentration. This indicates a reduction in transferrin attributable to starvation or an elevation in its urinary excretion. as well as the development of end-stage renal disease (ESRD) in diabetic kidney disease (DKD)[16].

In contrast, serum iron levels were significantly reduced in patients with DKD (82.833 ± 50.662 µg/dL) relative to the control group (104.349 ± 14.832 µg/dL, p = 0.0023). This observation indicates that modifications in iron metabolism are potentially linked to chronic inflammatory responses in DKD[17] The progression of diabetic kidney disease (DKD) is also attributed to ferroptosis, a novel form of programmed cell death induced by the intracellular accumulation of iron-dependent lipid peroxidation and other enzymes.[18] Iron deficiency anemia and the effectof a low-iron diet on renal gene expression are adversely correlated with diabetic kidney disease (DKD)[15].

The results revealed elevation in serum phosphorus levels in the Diabetic Kidney Disease (DKD) group compared to the control group. The average serum phosphorus level increased from 3.228 mg/dL to 5.055 mg/dL, demonstrating substantial statistical significance (p = 0.0003). This indicates that the disparity is not coincidental but rather signifies a true correlation between increased phosphorus levels and DKD.The, which are essential for regulating phosphorus concentrations in the body. As DKD advances, the capacity of the kidney to eliminate phosphorus diminishes, resulting in increased phosphorus buildup in the circulation. There is a significant correlation between phosphorus metabolism, FGF23 levels, and osteoporosis in patients with diabetic renal disease[19]. Additionally, DKD may exhibit increased susceptibility to elevated levels of FGF23, which may result in alterations in the metabolism of serum phosphorus .[20]

Hyperglycemia induces oxidative stress, which subsequently influences FGF23 levels, thereby affecting phosphorus metabolism. This is nearly identical to what researchers have verified [21] . Monitoring serum phosphorus levels is an important independent mortality risk factor in individuals with chronic kidney disease (CKD). A study indicated that increasing serum phosphorus concentrations were strongly correlated with an increased risk of mortality and a greater risk of cardiovascular-related mortality.[22].Estimated glomerular filtration rate (eGFR) is a conventional biomarker used to evaluate renal function in individuals with diabetes. eGFR predominantly depends on blood creatinine concentrations but is constrained in identifying early-stage kidney disease, as notable reductions in eGFR generally manifest only after considerable impairment of renal function[23,24] .

The CKD-EPI equation was used, **(Chronic Kidney Disease Epidemiology Collaboration Equation)** [25] . signifies possibly disruptions in iron availability, possibly resulting from chronic inflammation or compromised absorption and distribution pathways. Initially, this decrease may seem inconsistent with the concept of employing these cytokines as diagnostic biomarkers, as biomarkers associated with diseases are generally anticipated to be raised. The diagnostic significance of a biomarker is dictated by the extent of the disparity in its levels between ill and healthy individuals, rather than merely by elevation. In numerous disorders, elevation or reduction of specific biomarkers has been employed as a diagnostic instruments.

The markable decrease in IL-40 and IL-41 levels in patients with DKD relative to the control group may be attributed to the deregulation of immunological or inflammatory responses. This may be ascribed to the intricate metabolic and physiological characteristics of diabetes, indicate that IL-40 and IL-41 function as differentiating biomarkers between healthy individuals and those with diabetic kidney disease (DKD). In diagnostics, biomarkers need not be increased to be beneficial; the critical factor is the unambiguous differentiation

between sick and healthy individuals. An established example is insulin levels in type 1 diabetes mellitus (T1DM), where the condition is characterized by diminished insulin levels rather than elevated levels. The reduction in IL-40 and IL-41 levels in DKD patients compared to the control group represents a significant and potentially valuable diagnostic marker. Previous studies have demonstrated that IL-40 is involved in inflammatory and immune-mediated conditions, such as rheumatoid arthritis[26] .

The results of our Receiver Operating Characteristic (ROC)curve study further validated the diagnostic efficacy of these cytokines, with IL-41 demonstrating a significant ability to differentiate between DKD patients and healthy persons. The area under the curve (AUC) for IL-41 was 98.394%, indicating exceptional diagnostic precision. This strongly indicates that the considerable decrease in IL-40 and IL-41 levels may function as a dependable diagnostic criterion for differentiating DKD patients from the general populace.Diabetic kidney disease arises from sustained hyperglycemia-induced damage to renal microvasculature, resulting in chronic inflammation, oxidative stress, and fibrosis.[27].

These pathophysiological alterations may modify cytokine dynamics, either by diminishing their systemic availability due to excessive local consumption or by influencing their synthesis by immune cells.[28]. Consequently, the observed decline in IL-40 and IL-41 may reflect an exhausted immune response in the setting of chronic renal inflammation, rather than an absence of inflammatory activity.

CONCLUSION

The significant reduction of interleukin-40 (IL-40) and interleukin-41 (IL-41) observed in patients with diabetic kidney disease (DKD) suggests a potential role for these cytokines as immunological biomarkers linked to disease progression. Their altered expression may reflect underlying inflammatory and immunoregulatory effect associated with DKD pathogenesis. Incorporating the measurement of IL-40 and IL-41 levels—alongside established inflammatory and renal markers—could improve the early detection, risk stratification, and clinical management of DKD. Future longitudinal studies are warranted to validate these findings and explore their prognostic and therapeutic implications in diabetic nephropathy.

Declaration

Funding Statement: Nil

Ethical Compliance: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards .

Data Access Statement: Research data supporting this publication are available at located

Conflict of Interest declaration: we declare that have no affiliations with or involvement in any organization or entity with any financial interest in the subject matter or materials discussed in this manuscript.

Authors contribution:

HAR: Conceptualization, methodology, formal analysis, and manuscript writin, Data collection, investigation, and software analysis..

SMJ: Supervision, project administration, and final manuscript review

MMA: Literature review, validation, and manuscript editing

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