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The Role of Some Biochemical Markers in the Pathogenesis of Diabetic Nephropathy

Daroon Essam Raffik[1, a)], Amina Hamed Ahmed[2, b)] and Abdullah Adil Raoof[2, c)]

[1]*University of Kirkuk, College of Science, Department of Chemistry, Kirkuk, Iraq.*
[2] *Kirkuk University College of Medicine [KUCOM], Kirkuk, Iraq.*

a) *Corresponding author: daroonessam@uokirkuk.edu.iq*
b)*aminahamed2007@uokirkuk.edu.iq*
c)*dr.abdullahkoprulu@uokiruk.edu.iq*

Abstract. One of the main causes of end-stage renal disease worldwide is diabetic nephropathy (DN). For prompt intervention and better patient outcomes, early detection of biochemical markers linked to DN pathogenesis is essential. Objectives: the pathophysiology of diabetic nephropathy was examined in relation to inflammatory indicators (C-reactive protein [CRP], tumor necrosis factor-alpha [TNF-α]), α-Klotho, and glycemic control markers (glycated hemoglobin [HbA1c], glycated albumin, and ractopamines).. Methods: Between October 2024 and April 2025, a six-month cross-sectional study was carried out at Azadi Teaching Hospital and Kirkuk Teaching Hospital. 360 individuals were carefully split into four groups for the study: 90 patients with diabetes who did not have nephropathy, 90 patients with chronic renal disease (CRD), 90 patients with diabetic nephropathy, and 90 healthy controls. Standardized laboratory procedures were used to analyze biochemical parameters. Analysis of variance (ANOVA), post-hoc testing, correlation analysis, and multivariate regression analysis were all included in the statistical analysis. TNF-α concentrations (204.13 ± 86.17 p_g/mL vs. 32.28 ± 13.97 p_g/mL, $p<0.001$) and CRP levels (14.27 ± 4.01 mg/L vs. 4.48 ± 1.58 mg/L, $p<0.001$) were substantially higher in diabetic patients with nephropathy than in controls. Patients with diabetic nephropathy had significantly lower α-Klotho levels (201.27 ± 81.42 p_g/mL compared to 1173.04 ± 271.04 p_g/mL in controls, $p<0.001$). Glycated albumin showed a stronger association with diabetic complications ($r=0.78$, $p<0.001$) among glycemic control indicators than ractopamines ($r=0.44$, $p<0.01$) and HbA1c ($r=0.61$, $p<0.001$). The pathophysiology of diabetic nephropathy is significantly influenced by inflammatory indicators and α-Klotho deficiency. Compared to conventional glycemic indicators, glycated albumin seems to be a more sensitive and trustworthy indicator for evaluating glycemic control in individuals with diabetic nephropathy.

Keywords: Diabetic nephropathy, inflammatory markers, α-Klotho, glycated albumin, CRP, TNF-α

INTRODUCTION

One of the most severe microvascular consequences of diabetes mellitus is diabetic nephropathy (DN), which affects 20-40% of diabetic individuals and is the primary cause of end-stage renal disease (ESRD) worldwide. Diabetic nephropathy is a microvascular complication that affects people with type 1 diabetes (T1D) and type 2 diabetes (T2D). It shows up as a progressive loss in glomerular filtration rate (GFR) and persistent albuminuria. Diabetic nephropathy is becoming more and more prevalent worldwide, with major socioeconomic implications for healthcare systems everywhere. Complex, multifactorial interactions, including hemodynamic changes, metabolic abnormalities, and inflammatory cascades, are hallmarks of the pathophysiology of DN. These interactions eventually come together to cause progressive renal tissue destruction and functional decline[1]. Glycemic control has been the main emphasis of the conventional

paradigm of managing diabetic nephropathy, with HbA1c acting as the key biomarker for tracking the effectiveness of treatment. This strategy has been seriously called into question by new data, which show that the pathophysiology of DN goes far beyond straightforward hyperglycemic damage. Recent studies have demonstrated the crucial role that chronic inflammation plays in the development and course of diabetic nephropathy, with inflammatory mediators acting as both potential therapeutic targets and pathogenic drivers [2]. Targeting oxidative stress and chronic inflammation, two pathogenic mechanisms that are crucial to the etiology and development of DN, is a potentially effective treatment approach. Due to a wealth of clinical and experimental data showing that patients with diabetic nephropathy have higher levels of inflammatory biomarkers than those without renal dysfunction, the inflammatory hypothesis of DN has gained significant traction [3]. Studies have shown that protein oxidation measures are useful in evaluating the course of the disease and the effectiveness of treatment, making them important markers of oxidative stress in diabetic complications [4]. These characteristics may be used as novel biomarkers for the early detection and monitoring of renal injury, and they offer important insights into the molecular mechanisms driving diabetic nephropathy Among the inflammatory mediators linked to the pathophysiology of diabetic nephropathy, tumor necrosis factor alpha (TNF-a) and C-reactive protein (CRP) have been identified as particularly significant contributors to the development and progression of the disease. A pro-inflammatory condition that is favorable to oxidative stress is produced by upregulating the gene transcription of inflammatory mediators, including IL-1, IL-6, IL-7, IL-8, and TNF-a. The chronic inflammatory state that underlies diabetic patients with nephropathy is reflected in the constantly high levels of C-reactive protein, an acute-phase reactant that is largely generated by hepatocytes in response to inflammatory stimuli. Urinary albumin excretion is independently linked to increased inflammatory markers in early type 2 diabetic nephropathy.

A pleiotropic cytokine with a variety of biological roles, TNF-α promotes endothelial dysfunction, increases vascular permeability, and contributes to insulin resistance, all of which are key components of the inflammatory cascade. Inflammatory markers such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), systemic immune-inflammation index (SII), and red blood cell distribution width (RDW) have been suggested as possible predictors of DN development, as evidenced by recent retrospective studies and meta-analyses[5]. Our knowledge of the pathophysiology of diabetic nephropathy has been completely transformed by the identification and description of a-Klotho as an anti-aging protein with strong renal protective qualities. A protein recognized for its anti-aging qualities, a-Klotho has been demonstrated to postpone the onset of age-related illnesses. a-Klotho was first discovered to be a gene whose absence causes mice to age more quickly. Since then, it has been understood to be a multipurpose humoral factor with a wide range of biological functions, such as Controlling mineral metabolism, preserving vascular integrity, and regulating inflammatory reactions. In both humans and animals, early diabetic nephropathy has been consistently associated with decreased renal a-Klotho expression. This suggests that a-Klotho deficiency may occur before overt nephropathy develops. a-Klotho has a variety of Reno protective mechanisms, including direct modulation of tubular and glomerular function, antioxidant qualities, and anti-inflammatory actions. A multifunctional protein called Klotho (KL) has been shown to have Reno protective effects. Experimental research indicates that supplementing with Klotho can reduce diabetic kidney damage in several ways. Recent studies have demonstrated that klotho stimulates AMPK-PGC1a expression to have a mitochondria-protective impact in diabetic kidney disease, underscoring the intricate molecular underpinnings behind its renoprotective properties [6]. There is ongoing clinical research and discussion over the best method for glucose monitoring in individuals with diabetic nephropathy. Despite being the gold standard for glycemic assessment for many years, HbA1c has shown limits in certain patient populations, especially those with chronic renal disease. In contrast to HbA1c, glycated albumin (GA) indicates both postprandial PG levels and short-term glycemic management. Alternative glycemic biomarkers may be required because to the substantial impact that chronic kidney disease-related changes in protein metabolism, anemia, and red blood cell turnover can have on HbA1c reliability. In contrast to HbA1c, which measures glycemic control over a longer period of time (2–3 months), glycated albumin has become a viable substitute indication. Glycemic state over the previous two to three weeks is reflected in glycated albumin, the precursor of advanced glycation end products, which actually performs better at glycemic monitoring than HbA1c. Glycated albumin is the preferable sign for evaluating glycemic control in advanced chronic renal disease, according to multiple studies. It has a better connection with data from continuous glucose monitoring than HbA1c. Additionally, regardless of HbA1c, variability in GA may be a more accurate indicator of the development of diabetic nephropathy in type 2 diabetic patients, indicating its potential use for risk stratification as well as glycemic surveillance[7,8]. Patients with diabetic nephropathy have also been studied for fructosamine,

another potential glycemic biomarker that reflects glycemic control over 1-2 weeks, although the results have been less reliable than those of glycated albumin. Since the GA/HbA1c ratio is linked to diabetic retinopathy but not diabetic nephropathy in type 2 diabetic patients, the relationship between these various glycemic indicators and diabetic complications is still complicated. This suggests that different glycemic indicators may be useful for different diabetic complications. It is assumed that renal anemia and proteinuria, respectively, have an impact on HbA1c and GA in patients with diabetic nephropathy (DN) as the disease progresses, underscoring the intricate relationships between renal function and the accuracy of glycemic biomarkers [9]. The care of diabetic nephropathy has undergone a paradigm shift toward precision medicine with the incorporation of inflammatory markers, a-Klotho evaluation, and improved glucose monitoring. This all-encompassing strategy acknowledges the limits of conventional single-biomarker approaches as well as the complex nature of DN etiology. To improve patient outcomes and create focused treatment interventions, it is essential to comprehend the intricate interactions between inflammation, hyperglycemia, and protective factors like a-Klotho [10] .The goal of the current work is to present a thorough examination of these biochemical indicators in the pathophysiology of diabetic nephropathy, examining both their individual and combined roles in the development and progression of the disease [11].This study aims to improve our knowledge of DN pathophysiology and guide evidence-based clinical practice by investigating the connections between inflammatory markers, a-Klotho levels, and other glycemic control indicators in various patient populations. The results of this study could help create new diabetic nephropathy diagnostic algorithms, risk assessment instruments, and treatment goals, which would ultimately enhance the treatment and outcomes for patients with this debilitating condition [12].

PATIENTS AND METHODS

This study was cross-sectional in nature 360 people were recruited and divided into four groups: 90 patients with diabetic nephropathy, 90 patients with chronic kidney disease (non-diabetic CRD), 90 patients with type 2 diabetes mellitus without nephropathy, and 90 healthy controls without either kidney disease or diabetes. Participants between the ages of 18 and 75 and who had a stable clinical condition and a verified diagnosis of either type 2 diabetes mellitus or chronic renal disease were eligible. People with active infections, inflammatory diseases, cancers, recent hospitalizations, acute renal injury, type 1 diabetes, and pregnancy were not included. Information on demographics, such as age, gender, and place of residence, was gathered via structured interviews, and blood pressure and anthropometric measurements were taken according to conventional protocols. A 12-hour overnight fast was followed by the collection of fasting blood samples to evaluate several metabolic markers. Exuctosamine, glycated albumin, and HbA1c were examples of glycemic indicators. Serum creatinine, blood urea nitrogen, estimated glomerular filtration rate (eGFR), and microalbuminuria were used to assess renal function. Tumor necrosis factor-alpha (TNF-a) and C-reactive protein (CRP) were examples of inflammatory indicators, and a-Klotho was one of the other parameters assessed.

STATISTICAL ANALYSIS

SPSS version 26.0 was used to conduct the statistical analysis. For continuous variables, data were presented as mean ± standard deviation; for categorical variables, frequencies were presented as percentages. The post-hoc Tukey's test was performed for multiple comparisons after the means of the groups were compared using a one-way ANOVA. To evaluate the correlations between variables, a Pearson correlation analysis was used. P-values less than 0.05 were regarded as statistically significant.

RESULTS

Demographic Characteristics

The average age of the 360 participants in the study was 58.5±15.2 years. There were 198 females (53.6%) and 162 males (46.0%) in the demographic distribution. 75% of participants (25.0%) reported living in a rural area, whereas 198 individuals (55.0%) reported living in an urban area.

TABLE 1. Demographic characteristics of study participants

Parameter	Diabetes (n=90)	Kidney Disease (n=90)	Diabetes with Kidney Disease (n=90)	Healthy Controls (n=90)
Age (years)	58.0±18.05	54.0±20.17	58.0±22.64	39.0±10.0
Gender				
Male	45 (50.0%)	50 (55.6%)	48 (53.3%)	24 (26.7%)
Female	45(50.0%)	40 (44.4%)	42 (46.7%)	66 (73.3%)
Residence				
Rural	21 (26.7%)	17 (18.9%)	17 (18.9%)	17 (18.9%)

Inflammatory Markers Analysis

The research groups' levels of TNF-α and CRP increased gradually, according to the examination of inflammatory markers. Compared to diabetic patients without nephropathy (6.84±1.99 mg/L), nephropathy patients without diabetes (9.45±2.61 mg/L), and healthy controls (4.48±1.58 mg/L), diabetic patients with nephropathy had significantly higher CRP levels (14.27±4.01 mg/L) ($p<0.001$). Likewise, TNF-α levels were significantly higher in the group with diabetic nephropathy (204.13±86.17 pg/mL) than in any other group. In comparison to controls (32.28±13.97 pg/mL), the diabetes group had moderately raised TNF-α levels (84.21±25.36 pg/mL), while the nephropathy group had intermediate elevation (159.41±71.03 pg/mL).

TABLE 2. Distribution of Study Participants by CKD Stage Based on eGFR

CKD Stage	eGFR Range (mL/min/1.73m²)	Diabetic (n=90)	Nephropathy (n=90)	Diabetes with Nephropathy (n=90)	Control (n=90)	Total (n=360)
Stage 1	≥90	45 (50.0%)	15 (16.7%)	8 (8.9%)	85 (94.4%)	153 (42.5%)
Stage 2	60-89	35 (38.9%)	25 (27.8%)	15 (16.7%)	5 (5.6%)	80 (22.2%)
Stage 3a	45-59	8 (8.9%)	30 (33.3%)	25 (27.8%)	0 (0.0%)	63 (17.5%)
Stage 3b	30-44	2 (2.2%)	15 (16.7%)	28 (31.1%)	0 (0.0%)	45 (12.5%)
Stage 4	15-29	0 (0.0%)	5 (5.6%)	12 (13.3%)	0 (0.0%)	17 (4.7%)
Stage 5	<15	0 (0.0%)	0 (0.0%)	2 (2.2%)	0 (0.0%)	2 (0.6%)

*CKD staging based on KDIGO 2012 guidelines using estimated glomerular filtration rate (eGFR). Data presented as number (percentage) of participants in each stage.

TABLE 3. Comparison of Inflammatory Markers Between Study Groups

Group	CRP (mg/L)	TNF-α (pg/mL)	P-value for CRP	P-value for TNF-α
Healthy Controls (n=90)	4.48±1.58[a]	32.28±13.97[a]	-	-
Diabetes (n=90)	6.84±1.99[b]	84.21±25.36[b]	<0.001	<0.001
Kidney Disease (n=90)	9.45±2.61[c]	159.41±71.03[c]	<0.001	<0.001
Diabetes with Kidney Disease (n=90)	14.27±4.01[d]	204.13±86.17[d]	<0.001	<0.001

*Different superscript letters indicate statistically significant differences ($p<0.05$) using Tukey post-hoc test

α-Klotho

The degree of disease was significantly inversely correlated with α-Klotho levels. When compared to healthy controls (1173.04±271.04 pg/mL), the diabetic nephropathy group had the lowest α-Klotho levels (201.27±81.42 pg/mL), an 82.9% decrease. While nephropathy patients without diabetes maintained

comparatively higher levels (842.29±198.77 pg/mL), diabetic patients without nephropathy displayed an intermediate decline (547.17±172.09 pg/mL).

Table 4: Comparison of α-Klotho Levels Between Study Groups

Group	α-Klotho (pg/mL)	Percentage Change vs. Controls	P-value
Healthy Controls (n=90)	1173.04±271.04[a]	-	-
Diabetes (n=90)	547.17±172.09[b]	-53.4%	<0.001
Kidney Disease (n=90)	842.29±198.77[c]	-28.2%	<0.001
Diabetes with Kidney Disease (n=90)	201.27±81.42[d]	-82.9%	<0.001

*Different superscript letters indicate statistically significant differences (p<0.05)

Glycemic Control Markers Comparison

Different patterns emerged from the comparison of glycemic control markers: Diabetes patients (7.31±2.84%), nephropathy patients (6.98±2.07%), and controls (4.68±2.08%) had the lowest HbA1c levels, while diabetic nephropathy patients had the highest (10.86±3.44%). Compared to diabetic patients (408.61±210.84%) and controls (124.08±87.23%), glycated albumin was most significantly elevated in diabetic nephropathy patients (908.61±370.04%), and in nephropathy patients as well (742.04±518.69%). Patients with diabetes had the greatest amounts of fructosamine (9.17±2.61 μmol/L), while those with nephropathy and diabetic nephropathy had lower levels (4.51±1.52 μmol/L and 3.08±1.62μmol/L) than controls (2.51±0.43μmol/L).

TABLE 5. Comparison of Glycemic Control Markers Between Study Groups

Group	HbA1c (%) (N.r)	Glycated Albumin (%)(N.r)	Fructosamine (μmol/L) (N.r)
Healthy Controls (n=90)	4.68±2.08[a]	124.08±87.23[a]	2.51±0.43[a]
Diabetes (n=90)	7.31±2.84[b]	408.61±210.84[b]	9.17±2.61[b]
Kidney Disease (n=90)	6.98±2.07[b]	742.04±518.69[c]	4.51±1.52[c]
Diabetes with Kidney Disease (n=90)	10.86±3.44[c]	908.61±370.04[d]	3.08±1.62[d]
P-value	<0.001	<0.001	<0.001

Different superscript letters indicate statistically significant differences (p<0.05)

DISCUSSION

The current investigation offers thorough proof of the complex pathophysiology of diabetic nephropathy, demonstrating the important roles that inflammatory mediators, a-Klotho deficiency, and altered glycemic control markers play in the onset and progression of the illness. When comparing diabetic nephropathy patients to healthy controls, our results reveal a striking 700% increase in CRP levels and a 536% increase in TNF-a levels. This is consistent with recent systematic reviews that demonstrate the effectiveness of inflammatory markers as reliable indicators of the course of diabetic nephropathy [13]. These inflammatory alterations align with the current concept that diabetic nephropathy is a complex inflammatory illness involving several cytokine pathways rather than just being a result of hyperglycemic damage. Our study's observation of a dose-dependent relationship between systemic inflammation and disease severity, as well as recent findings showing that oxidative stress and chronic inflammation are key factors in the pathophysiology of diabetic nephropathy, is supported by the progressive elevation of inflammatory markers from diabetic patients to diabetic nephropathy patients [14]. The intermediate levels of inflammatory markers in the nephropathy-only group suggest that chronic kidney disease itself promotes inflammatory cascades, but the magnified inflammatory responses observed in the diabetic effect of diabetic nephropathy patients indicate a

synergistic inflammatory environment that accelerates disease progression, consistent with recent evidence showing that gene expression of inflammatory mediators such as IL-1, IL-6, IL-7, IL-8, and TNF-α are significantly increased in diabetic patients, creating a proinflammatory state [15]. One of the most significant biomarker changes found in this study is the significant 82.9% decrease in a-Klotho levels seen in our diabetic nephropathy patients. This finding supports the growing idea that a-Klotho is a crucial renoprotective factor whose deficiency contributes to the pathophysiology of diabetic nephropathy. This result is in line with new studies showing that a-Klotho has anti-aging qualities and can postpone the onset of age-related illnesses in both people and animals, early diabetic nephropathy has been linked to decreased renal a-Klotho expression [16]. Since recent research has demonstrated that a-Klotho has renoprotective effects through multiple mechanisms, such as mitochondrial protection via AMPK-PGC1a expression, podocyte injury prevention through TRPC6 channel targeting, and anti-inflammatory effects, the mechanism underlying this dramatic a-Klotho deficiency most likely involves multiple pathways [17]. As a possible early biomarker for diabetic kidney disease risk assessment, the intermediate a-Klotho levels found in diabetic patients without nephropathy in our study imply that a-Klotho deficiency may occur before overt nephropathy develops. With levels 630% higher than controls, our comparative analysis of glycemic control markers showed that glycated albumin had superior sensitivity in identifying glycemic control problems in patients with diabetic nephropathy This finding is consistent with recent meta-analyses that indicate glycated albumin performs better than HbA1c for glycemic monitoring in patients with chronic kidney disease (CKD) [18]. This finding is especially noteworthy because, in contrast to HbA1c, glycated albumin represents postprandial glucose levels and shorter-term glycemic control, making it less vulnerable to the confounding effects of anemia and altered red blood cell turnover, which frequently occur in chronic kidney disease [19]. Although glycated albumin is still the preferred marker for evaluating glycemic control in advanced chronic kidney disease, recent research indicates that it may be influenced by factors other than glycemic control, such as changes in protein metabolism in kidney disease. These findings are consistent with the elevated glycated albumin levels seen in both diabetic patients and nephropathy patients without diabetes [20]. Recent evidence suggests that fructosamine may be less dependable in this population than glycated albumin. This is supported by the contrasting pattern of fructosamine, which showed lower levels in nephropathy groups and higher levels in diabetic patients. This pattern is likely due to the shorter half-life of proteins in patients with kidney disease. The identification of particular inflammatory pathways and a-Klotho deficiency as important characteristics of diabetic nephropathy suggests potential therapeutic targets for intervention, which is supported by recent preclinical evidence suggesting that anti-inflammatory interventions represent promising therapeutic strategies for diabetic nephropathy. As a result, the clinical implications of our findings go beyond biomarker identification to include novel therapeutic strategies [21]. In line with recent longitudinal studies showing that glycated albumin variability is a superior predictor of diabetic nephropathy progression in type 2 diabetic patients, the variability in glycated albumin levels seen in our study may be a better indicator of the progression of diabetic nephropathy independent of HbAlc levels [22].

CONCLUSIONS

This work highlights the complex pathophysiology of diabetic nephropathy, highlighting the critical roles of a-Klotho deficiency and chronic inflammation. The severity of the condition is correlated with elevated levels of inflammatory markers such as TNF-a and CRP, while a considerable decrease in a-Klotho (more than 80% when compared to healthy individuals) indicates its potential as a biomarker and therapeutic target. Furthermore, in afflicted patients, glycated albumin was found to be a more sensitive measure of glycemic management than either fructosamine or HbAlc. When considered as a whole, these results suggest that metabolic abnormalities, loss of protective proteins, and inflammatory processes are the primary causes of diabetic nephropathy, providing valuable insights for the development of targeted diagnostics and treatments.

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