RESEARCH PAPER

Biochemical Markers Associated with Diabetic Nephropathy in Patients with Type 2 Diabetes

Uzma Habib[1], Irfan Rasool[2], Rajesh Kumar[3], Ramsha Tehreem[4], Pervaiz Azam Malik[5], Qiyamov Baxtiyor Ergashovich[6]

[1]Lecturer, Swat College of Pharmaceutical Sciences, Swat, Pakistan
[2]Assistant Professor Nephrology, Department of Nephrology, Allied-II Hospital, Faisalabad Medical University, Faisalabad, Pakistan
[3]Associate Professor, Department of Medicine, Shaheed Mohtarma Benazir Bhutto Medical College Lyari & Sindh Govt: Lyari General Hospital, Karachi, Pakistan
[2]Senior Registrar Medicine, Sharif Medical and Dental College, Lahore, Pakistan
[5]Assistant Professor, Pathology Department, Rai Medical College Sargodha, Pakistan
[6]Department of Human Anatomy, Samarkand State Medical University, Samarkand, Uzbekistan

Corresponding author: Uzma Habib,
Lecturer, Swat College of Pharmaceutical Sciences, Swat, Pakistan
Email: uzmahabib7@hmail.com

ABSTRACT
The aim of this study was to evaluate the relationship of renal dysfunction, glycemic control, inflammatory cytokines and oxidative stress markers with the severity of diabetic nephropathy in T2DM patients. This analytical cross sectional study took place in hospital, and 180 patients with T2DM were separated into three groups according to the urine albumin-creatinine ratio (UACR), and estimated glomerular filtration rate (eGFR): normoalbuminuria, microalbuminuria and macroalbuminuria and/or reduced eGFR. Biochemical and ELISA methods was used to analyze the renal function parameters, glycemic markers, inflammatory markers (TNF-α, IL-6, hs-CRP), and oxidative stress markers (MDA, SOD, GSH). The statistical analysis was done by SPSS version 25.0. The more severe the nephropathy, the greater was the progressive loss of renal function and worsening of glycemic control ($p<0.001$). All inflammatory cytokines and oxidative stress marker MDA were significantly higher among all study groups and antioxidant markers SOD and GSH were significantly lower among all study groups ($p<0.001$). The analysis identified a favorable association between the variables of UACR with HbA1c, TNF-α, IL-6 and MDA, and a significant negative correlation of eGFR. Multivariate logistic regression revealed IL-6, TNF-α and MDA as independent factors for diabetic nephropathy. Diabetic nephropathy is to be driven by chronic inflammation and oxidative stress. These biomarkers may help detect and track diabetes progression in patients.
Keywords; Type 2 Diabetes Mellitus; Diabetic Nephropathy, IL-6; TNF-α; MDA; and Oxidative Stress; Inflammation
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1. INTRODUCTION

Diabetes Mellitus is a long-term metabolic condition that involves a progressive loss of insulin sensitivity, decline of pancreatic cells function which leads to chronic hyperglycemia [1]. Insulin resistance is a phenomenon in which peripheral tissues show have reduced sensitivity to insulin, resulting in decreased glucose uptake and increasing the production of glucose in the liver by gluconeogenesis. Pancreatic β-cells do not meet this demand for insulin over time, leading to a relative lack of insulin and persistent hyperglycemia [2]. The pathogenesis and course of T2DM is complex and multifactorial and involves genetic susceptibility, obesity, lack of exercise and chronic low-grade systemic inflammation [3, 4].

These biochemical changes caused by persistent hyperglycemia are elevated oxidative burden within the system [5]. All these pathways converge to endothelial dysfunction and vascular injury and microvascular complications like diabetic nephropathy (DN). One of the most severe complications of T2DM is DN and its defining features are the presence of chronic albuminuria, declining filtration, and eventual progression into end-stage renal disease. This is a huge health problem all around the world due to the high morbidity, mortality and health care cost [6]. Metabolic imbalance is not

the only factor involved; inflammatory mechanisms and oxidative stress also participate in the pathogenesis of diabetic nephropathy. The oxidative stress caused by hyperglycemia results in generation of ROS that trigger damage of kidney cells [7]. At the same time, activation of inflammatory signaling pathways enhanced cytokine expression and discharge that worsens renal injury and contribute to fibrotic changes of renal tissue [8].

The previous studies have shown that diabetic nephropathy is not simply a hemodynamic disorder, but rather multiple metabolic, inflammatory, and oxidative mechanisms are involved [9]. Early diagnosis, however, can be difficult because most common laboratory markers like serum creatinine and eGFR are abnormal only when the disease is more advanced [10]. Diabetic nephropathy had been reported to be associated with individual biomarkers such as serum creatinine, HbA1c, TNF-α and IL-6 in the previous literature. For instance, the inflammatory pathways have been shown by previous work to be important in the deterioration of renal function over time, and oxidative stress has been pointed out as a major mechanism in diabetic renal injury [11]. Likewise, previous research showed that albuminuria and loss of eGFR are strong indicators of the progression of renopathy [12]. Most of the previous studies, however, are limited to the evaluation of a single biomarker and do not consider a multi-pathway approach. There has been, however, limited research that has evaluated renal function markers, inflammatory cytokines and oxidative stress parameters in the same study population. Furthermore, no independent predictors of diabetic nephropathy were identified using multivariate analysis that included all three pathological domains [13].

A major research gap exists regarding the integrated biochemical profile of the progression of diabetic nephropathy, particularly in resource-limited areas where early biochemical markers may assist in clinical decision-making processes. Thus, it is imperative to identify tests for early detection and prediction of diabetic nephropathy that are reliable biochemical, inflammatory, and oxidative stress markers. These biomarkers are used in conjunction with one another, which may help to better stratify the risk level in diabetes in patients and help to determine the appropriate time for therapeutic intervention.

2. METHODOLOGY

2.1. Study design

It was hospital based analytical cross-sectional study. The study was carried out over a specified time period from April 2025 to March 2026 in the Swat College of Pharmaceutical Sciences.

2.2. Study participants

The total number of patients was n=180 and the sample size was determined at 95% confidence level with a 5% error margin. Participants were classified into three groups according to the UACR: <0.3, 0.3-0.5, >0.5 and estimated glomerular filtration rate (eGFR) using the CKD-EPI equation: <55, 55-70, and >70. In group A, diabetic patients had no renal involvement (normoalbuminuria, UACR <30 mg/g), and maintained renal function with eGFR ≥90 mL/min/1.73 m². Patients who had early renal involvement (microalbuminuria) (UACR 30-300 mg/g, eGFR ≥ 60 mL/min/1.73 m²) were included in Group B. Patients with established renal involvement, that is, macroalbuminuria (UACR >300 mg/g) and/or reduced renal function (eGFR <60 mL/min/1.73 m²) were included in group C. Patients included in the study had a minimum duration of T2DM of ≥1 year and were aged between 30-70 years. Patients with diabetes 1, acute or chronic infections, non-diabetic kidney disease, hepatic failure, malignancy, autoimmune disease, pregnancy or patients receiving nephrotoxic agents were excluded.

2.3. Data collection

Venous blood was collected after an overnight fast from each subject in an aseptic manner, in a volume of about 5-10 ml. They were then centrifuged at 3000 rpm for 10 minutes and the separated serum was kept at −20°C until biochemical analysis was carried out. Urine samples were taken for the measurement of urine albumin-creatinine ratio. Serum creatinine, blood urea, and estimated glomerular filtration rate (eGFR) were used to assess renal function parameters, and glycemic parameters such as fasting blood glucose and glycated hemoglobin (HbA1c) were used to assess glycemic parameters. Standardized enzyme-linked immunosorbent-assays (ELISA) were used to measure the levels of TNF-α, IL-6, and the high-sensitivity C-reactive protein (hs-CRP). Oxidative stress was assessed by measuring included SOD, MDA, and GSH spectrophotometrically. All biochemical assays were done according to the manufacturer's specifications and calibration and quality control procedures were carried out to assure the accuracy and reproducibility of the assay.

2.4. Statical Analysis

Data analysis was done by SPSS 25.0 software. The data was presented as mean ± standard deviation for continuous variables and frequency (%). One-way analysis of variance (ANOVA) was performed for intergroup comparisons and Tukey's test was used as needed. Pearson or Spearman correlation was used for the biochemical parameters to see the association with renal function parameters. In addition, multivariable logistic regression was used to identify the independent factors associated with diabetic nephropathy while controlling for other potential

confounding factors such as age, sex, duration of diabetes and HbA1c level. A p value < 0.05 was set as the criteria for significance.

3. RESULTS

The total number of enrolled subjects was 180 who were randomly divided into three groups (60 patients in each group). There was a significant difference between the groups in mean age with diabetic nephropathy more prevalent in older age (Group A: 52.4 ± 8.6 years, Group C: 58.7 ± 8.3 years; p = 0.01). Likewise, the length of diabetes was highly significantly greater in Group C (13.5 ± 4.2 years) than in Group A (6.2 ± 2.1 years) (p < 0.001). BMI also showed a significant upward trend from 26.8 ± 3.2 kg/m² in Group A to 29.4 ± 4.1 kg/m² in Group C (p = 0.02). The increase in HbA1c was statistically significant between groups, ranging from 7.1 ± 0.8% to 9.4 ± 1.2% (p < 0.001), and demonstrating an increase in glycemic control from 7.1% to 9.4% with the progression of the disease. No statistically significant variation was observed in the distribution of gender across the groups in Table 1.

Table 1: Baseline characteristics

Parameter	Group A (n=60)	Group B (n=60)	Group C (n=60)	p-value
Age (years)	52.4 ± 8.6	55.1 ± 7.9	58.7 ± 8.3	0.01
Duration of diabetes (years)	6.2 ± 2.1	9.8 ± 3.4	13.5 ± 4.2	<0.001
BMI (kg/m²)	26.8 ± 3.2	28.1 ± 3.6	29.4 ± 4.1	0.02
HbA1c (%)	7.1 ± 0.8	8.3 ± 1.0	9.4 ± 1.2	<0.001
Male, n (%)	32 (53.3%)	34 (56.7%)	35 (58.3%)	0.84

The renal function was significantly impaired in all study groups. Serum creatinine increased progressively from 0.89 ± 0.21 mg/dL in Group A to 2.18 ± 0.45 mg/dL in Group C (p < 0.001). Blood urea showed a similar rising pattern from 28.6 ± 6.4 mg/dL to 62.5 ± 10.9 mg/dL (p < 0.001). Importantly, eGFR was significantly lower in Group C (45.6 ± 9.7 mL/min/1.73m²) than in Group A (98.4 ± 12.5 mL/min/1.73m²) (p < 0.001) suggesting progressive renal loss of filtration. The UACR value rose significantly from 18.2 ± 6.5 mg/g to 412.6 ± 85.3 mg/g (p < 0.001) reflecting the presence of severe albuminuria in advanced disease in fig 1.

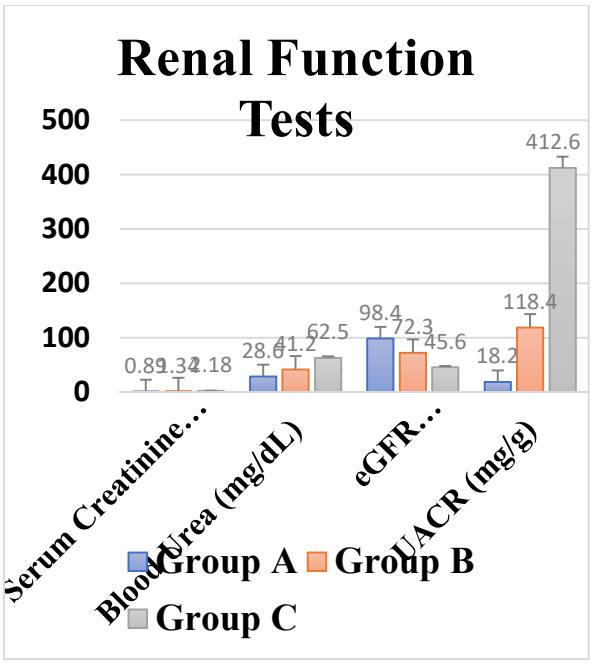

Figure 1: Renal function indicators were compared between the study groups, serum creatinine, blood urea and urinary albumin-to-creatinine ratio. The data was given as Mean ± SD.

Fasting blood glucose increased significantly from 138.5 ± 22.4 mg/dL in Group A to 198.3 ± 34.5 mg/dL in Group C (p < 0.001). Also, HbA1c increased significantly (p < 0.001) from a baseline of 7.1 ± 0.8% to 9.4 ± 1.2% in the transition to diabetic nephropathy, which indicates that poor long-term glycemic control is strongly linked to progression of diabetic nephropathy in fig 2.

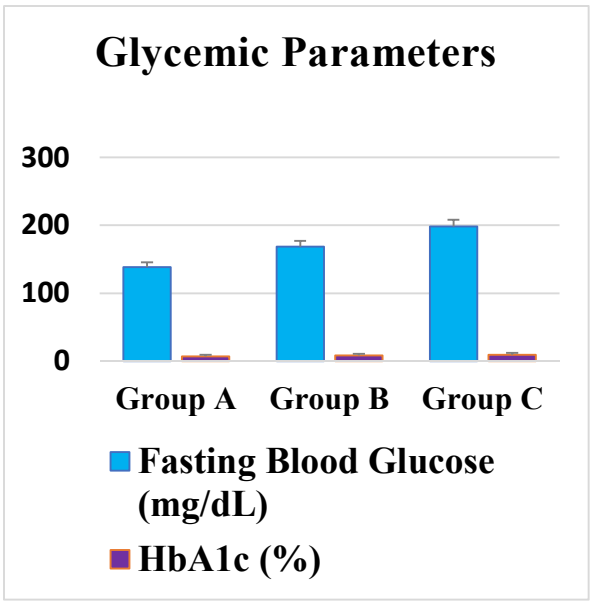

Figure 2: Comparison FBG and HbA1c levels of the study groups. Data are presented as mean ± SD. Statistical analysis was performed using one-way ANOVA followed by post hoc analysis. A p-value < 0.05 was considered statistically significant.

There was a significant increase in inflammatory cytokines. TNF-α increased from 18.5 ± 4.2 pg/mL in group A to 68.9 ± 9.5 pg/mL in group C and IL-6 showed a similar trend, increasing. hs-CRP increased .001), and GSH reduced from 7.9 ± 1.3 from 2.1 ± 0.6 mg/L to 12.9 ± 2.3 mg/L ($p < 0.001$). The results of this study clearly suggest a progressive relationship between the severity of diabetic nephropathy and systemic inflammation in Table 2.

Table 2: Serum Inflammatory Biomarkers

Marker	Group A	Group B	Group C	p-value
TNF-α (pg/mL)	18.5 ± 4.2	42.7 ± 6.8	68.9 ± 9.5	<0.001
IL-6 (pg/mL)	14.2 ± 3.5	38.6 ± 5.9	61.3 ± 8.7	<0.001
hs-CRP (mg/L)	2.1 ± 0.6	6.8 ± 1.4	12.9 ± 2.3	<0.001

In the advanced nephropathy, oxidative stress was significantly increased. The MDA levels were elevated in Group C (9.6 ± 1.8 nmol/mL) in comparison with Group A (2.8 ± 0.7 nmol/mL) ($p < 0.001$) which reflects increased lipid peroxidation. However, antioxidant defenses were found to be significantly reduced. SOD decreased from 8.7 ± 1.5 U/mL to 3.4 ± 0.9 U/mL ($p < 0.001$), and GSH decreased; $p<0.001$. This is indicative of a definite imbalance between the oxidants and antioxidants in the advancement of diabetic nephropathy in Table 3.

Table 3: Oxidative Stress and Antioxidants

Parameter	Group A	Group B	Group C	p-value
MDA (nmol/mL)	2.8 ± 0.7	5.9 ± 1.2	9.6 ± 1.8	<0.001
SOD (U/mL)	8.7 ± 1.5	6.1 ± 1.2	3.4 ± 0.9	<0.001
GSH (µmol/L)	7.9 ± 1.3	5.2 ± 1.1	3.0 ± 0.8	<0.001

IL-6 showed the strongest correlation ($r = +0.74$, $p < 0.001$), followed by TNF-α ($r = +0.71$, $p < 0.001$) and MDA ($r = +0.69$, $p < 0.001$). The moderate positive correlation of HbA1c was also found ($r = +0.62$, $p < 0.001$). In contrast, the markers of disease severity were well correlated with eGFR ($r = −0.78$, $p < 0.001$), suggesting that inflammation and oxidative stress would have a negative association with renal function in table 4.

Table 4: Correlation of Clinical, Inflammatory, Oxidative Stress, and Renal Parameters with UACR

Marker	r value	p-value
HbA1c	+0.62	<0.001
TNF-α	+0.71	<0.001
IL-6	+0.74	<0.001
MDA	+0.69	<0.001
eGFR	−0.78	<0.001

Multivariable analysis revealed several independent factors associated with diabetic nephropathy. Among them, IL-6 emerged as the strongest predictor (OR = 1.63, 95% CI: 1.28–2.05, $p < 0.001$), followed by TNF-α (OR = 1.56, $p < 0.001$) and MDA (OR = 1.48, $p = 0.002$). HbA1c (OR = 1.42, $p = 0.003$) and duration of diabetes (OR = 1.31, $p = 0.01$) also demonstrated significant associations with the presence of diabetic nephropathy. These findings indicate that inflammatory mediators and oxidative stress markers contribute to the development of diabetic nephropathy beyond the influence of glycemic control in Table 5.

Table 5: Independent Predictors of Diabetic Nephropathy

Variable	OR	95% CI	p-value
HbA1c	1.42	1.12–1.78	0.003
TNF-α	1.56	1.21–1.98	<0.001
IL-6	1.63	1.28–2.05	<0.001
MDA	1.48	1.15–1.89	0.002
Duration of diabetes	1.31	1.08–1.62	0.01

4. DISCUSSION

The interaction between renal function markers and indicators of inflammation and oxidative stress with the severity of diabetic patients [14]. The results show a clear and statistically significant worsening of renal function, glycemic control, inflammatory condition, and oxidative stress from the different stages of the disease. These outcomes are consistent with the concept of diabetic nephropathy being a multifactorial process, initiated by chronic hyperglycemia, chronic inflammation and oxidative stress [15].

In the current study, serum creatinine and blood urea levels were found to significantly rise with increasing severity of the disease, and eGFR progressively decreased from Group A to Group C, while urine albumin-creatinine ratio (UACR) was found to increase significantly with the increasing severity of

the disease [16, 17]. The results of this study are in keeping with the classical diabetic nephropathy pathophysiology that in early phase is characterized by hyperfiltration of the glomeruli, followed by the development of glomerulosclerosis and a progressive decline in renal function. Similar findings were obtained by Adeva et al, who found that albuminuria is a powerful determinant of structural glomerular damage and decreased glomerular filtration in diabetic patients [18]. Likewise, other studies from Hong et al, found that renal injury is strongly related to a decline in eGFR in T2DM [19].

The finding that HbA1c kept increasing in all groups was another interesting aspect in this study, as an rise intensity of nephropathy was associated with worse long-term glycemic control. Lyssenko et al. also showed that persistent hyperglycemia is an important factor in the development of microvascular complications such as diabetic kidney disease [20]. Chronic hyperglycemia leads to increased production of advanced glycation, endothelial injury and progressive damage to the glomeruli, leading to poorer renal function with time [21].

In this study, inflammatory indicators were considerably raised in patients with progressed nephropathy, suggesting that inflammation is closely linked with the pathogenesis of the condition. This finding has been similarly observed by Mahmoud et al, who showed a close relationship between TNF-α and IL-6 with albuminuria and renal dysfunction in diabetic populations [22]. Furthermore, the studies of Cardiscian et al. have shown that persistent mild inflammation is linked to disease development of glomerular endothelial injury and tubulointerstitial fibrosis in diabetic kidney disease. The current results support the hypothesis that inflammatory cytokines are not just markers but rather are active mediators of renal damage [23].

There was significant increase in oxidative stress markers like malondialdehyde (MDA) in addition to a significant decrease in antioxidant enzymes like superoxide dismutase (SOD) and reduced glutathione (GSH). This imbalance suggests increased lipid peroxidation, and reduced antioxidant defense mechanisms in advanced nephropathy [24]. Darenskaya et al, reported similar results, showing that in diabetic patients with microvascular complications there is a significant increase a pro-fibrotic pathway that causes glomerular and tubular damage [25].

This study also showed strong positive correlations of UACR with inflammatory/oxidative markers and strong negative correlations of eGFR with these markers. This means that an increase in renal dysfunction is closely associated with systemic inflammation and oxidative stress. This correlation has been described in previous studies, showed that albuminuria was correlated positively with inflammatory cytokines and negatively with renal filtration function [26].

After controlling for confounding factors (age, duration of diabetes, HbA1c), multivariate logistic regression showed that IL-6, TNF-α and MDA were independent risk factors for diabetic nephropathy. This indicates that inflammation and oxidative stress pathways could be important mechanisms of disease progression in addition to glycemic control [27]. Similar evidence was offered by Li et al, who put his focus on the non-glycemic mechanisms of the progression of diabetic kidney disease, which includes inflammation and hemodynamic stress [28].

The results of this study lend strong support for a polyetiological pathophysiological model for “DN” for diabetic nephropathy. composed of chronic hyperglycemia, inflammatory processes, and oxidative stress. IL-6, TNF-α, and MDA are important independent markers, which could be used as early markers for risk stratification and disease monitoring.

5. CONCLUSION

Diabetic nephropathy is a strong associated parameter of progressive renal dysfunction, increased inflammatory activity, and increased oxidative stress. Among the various biomarkers tested, IL-6, TNF- α and MDA were identified as independent markers of the severity of the disease and hence can serve as a marker for early diagnosis in diabetic nephropathy patients.

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