Volume 4, Issue 5, 2026

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

GLYCEMIC CONTROL AS A PREDICTOR OF INCIPIENT NEPHROPATHY: AN ANALYSIS OF EARLY KIDNEY DYSFUNCTION MARKERS

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DOI: https://doi.org/10.5281/zenodo.20622463

Keywords
Diabetic nephropathy, HbA1c, Microalbuminuria, Albumin-to-creatinine ratio, Glycemic control, Renal dysfunction, eGFR, Type 2 diabetes mellitus

Article History
Received: 03 April 2026
Accepted: 15 May 2026
Published: 30 May 2026

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Abstract

Background: *Diabetic nephropathy (DN) is the leading microvascular complication of diabetes mellitus, progressively impairing renal function and ultimately leading to end-stage renal disease (ESRD). Glycemic control, particularly reflected by glycated hemoglobin (HbA1c), is widely recognized as the principal modifiable risk factor for DN. Early identification of incipient nephropathy is critical to prevent irreversible renal damage.*

Objective: *To evaluate the relationship between glycemic control markers (HbA1c, fasting blood sugar) and early renal dysfunction markers (serum creatinine, urea, blood urea nitrogen [BUN], and urine albumin-to-creatinine ratio [ACR]) in patients with type 2 diabetes mellitus, and to determine the diagnostic performance of HbA1c for predicting incipient nephropathy.*

Methods: *A hospital-based cross-sectional study was conducted at Riphah International University Faisalabad Campus involving 100 adult patients with type 2 diabetes mellitus over six months (November 2024 – April 2025). Biochemical parameters including HbA1c, fasting blood sugar (FBS), serum creatinine, serum urea, BUN, and urinary ACR were measured. Complete blood count (CBC) parameters were also assessed. Statistical analyses included independent t-tests, one-way ANOVA, Pearson correlation, simple and multiple linear regression, and receiver operating characteristic (ROC) curve analysis.*

Results: *Among 100 participants (mean age 51.0 ± 15.9 years; 50% male), 61% had uncontrolled glycemia (HbA1c ≥ 7%). Mean HbA1c was 8.14 ± 2.47% and mean FBS was 172.3 ± 45.0 mg/dL. Patients with uncontrolled glycemia demonstrated significantly higher serum creatinine (1.87 vs 1.29 mg/dL), urea (56.6 vs 36.0 mg/dL), and BUN (26.4 vs 16.8 mg/dL), with significantly lower eGFR (51.5 vs 68.8 mL/min/1.73 m²; all $p < 0.001$). Microalbuminuria was present in 76% of participants. HbA1c correlated significantly with serum creatinine ($r = +0.292$, $p = 0.003$), urea ($r = +0.308$, $p = 0.002$), BUN ($r = +0.307$, $p = 0.002$), and eGFR ($r = −0.288$, $p = 0.004$). ROC analysis demonstrated an AUC of 0.723 for HbA1c in predicting albuminuria, with an optimal cut-off of 7.20% (sensitivity 60%, specificity 87%). Hemoglobin emerged as the strongest independent predictor of urinary ACR in multivariable analysis (standardised $\beta = −0.364$).*

Conclusions: *Glycemic control strongly predicts early renal dysfunction in type 2 diabetic patients. HbA1c at a threshold of 7.2% effectively identifies incipient*

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

nephropathy. Integration of HbA1c, urinary ACR, eGFR, and hemoglobin provides a robust biochemical framework for early detection and monitoring of diabetic nephropathy in clinical practice.

1. INTRODUCTION

Diabetic nephropathy (DN) is the most significant microvascular complication of diabetes mellitus and remains the single leading cause of end-stage renal disease (ESRD) in developed and developing countries alike. Globally, diabetes mellitus affects more than 500 million people, and approximately 20–40% will develop diabetic kidney disease (DKD) at some stage during the course of their illness (Persson & Rossing, 2018). In Pakistan, where the prevalence of type 2 diabetes mellitus is among the highest in South Asia, the burden of DN is especially pronounced, and the majority of patients are diagnosed at advanced stages owing to limited access to early screening, appropriate therapy, and inadequate patient knowledge (Hassanein & Shafi, 2022).

The pathogenesis of DN is fundamentally driven by chronic hyperglycemia, which triggers multiple interconnected pathogenic pathways including oxidative stress, inflammation, activation of protein kinase C, and the production of advanced glycation end-products (AGEs). These mechanisms collectively cause glomerular hypertrophy, endothelial dysfunction, basement membrane thickening, mesangial expansion, and tubular injury. The natural history of DN classically progresses from glomerular hyperfiltration through microalbuminuria to overt proteinuria, and ultimately to declining glomerular filtration rate (GFR) and ESRD if appropriate intervention is not instituted in time (Cooper, 1998; Thomas et al., 2015).

Among the various biochemical markers used to characterize the early stages of diabetic kidney disease, glycated hemoglobin (HbA1c) and the urinary albumin-to-creatinine ratio (ACR) occupy the most prominent positions. HbA1c, reflecting integrated glycemic exposure over the preceding two to three months, is the cornerstone of long-term glycemic monitoring and risk stratification in diabetic patients (Hassanein & Shafi, 2022). Fasting blood sugar (FBS) provides a complementary measure of short-term glycemic status. The urinary ACR is widely regarded as the most sensitive early indicator of glomerular barrier injury, capable of detecting microalbuminuria well before the appearance of overt proteinuria or a measurable decline in creatinine-based eGFR (Garg et al., 2015; Mogensen, 1990).

Serum creatinine, serum urea, and blood urea nitrogen (BUN) are conventional markers of renal function whose sensitivity is limited in the early stages of DN, as significant nephron loss may occur before these markers cross traditional reference limits. Their elevation in the uncontrolled diabetic population therefore represents an intermediate or advanced stage of functional impairment that nevertheless benefits from early intervention (ElSayed et al., 2025). A complete blood count (CBC) provides supplementary information regarding the hematological consequences of chronic kidney disease in diabetes, particularly anemia of renal origin, which arises from erythropoietin deficiency, shortened erythrocyte lifespan, and iron sequestration driven by chronic inflammation.

Despite a large body of international literature on biomarkers of diabetic nephropathy, data from Pakistani tertiary care settings with integrated glycemic, renal, and hematological profiling are limited. The present study was designed to address this gap by conducting a comprehensive cross-sectional analysis of 100 patients with type 2 diabetes mellitus at Riphah International University Faisalabad Campus. The primary objectives were to evaluate the association between HbA1c-defined glycemic control and multiple renal dysfunction markers, to determine the diagnostic performance of glycemic markers for the detection of incipient nephropathy, and to propose a biochemical monitoring framework integrating glycemic, renal, and hematological parameters for early identification of DN in clinical practice.

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2. MATERIALS AND METHODS

2.1 Study Design and Setting

A hospital-based, single-centre, cross-sectional analytical study was conducted at Riphah International University Faisalabad Campus in collaboration with the Department of Biochemistry and a tertiary care diabetic clinic in Faisalabad, Pakistan. Sample collection, biochemical analysis, and data entry were completed over six months between November 2024 and April 2025. The study was approved by the Research Ethics Committee of Riphah International University and was conducted in accordance with the Declaration of Helsinki (World Medical Association, 2013). Written informed consent was obtained from all participants in Urdu and English.

2.2 Study Population

A total of 100 patients with established type 2 diabetes mellitus were enrolled using convenience sampling. Inclusion criteria comprised: adult patients with a documented diagnosis of type 2 DM of at least two years duration, age between approximately 30 and 80 years, attendance at the diabetic outpatient service, and willingness to provide informed consent. Patients were excluded if they had a pre-existing diagnosis of chronic kidney disease unrelated to diabetes, primary glomerular disease, active urinary tract infection, pregnancy, malignancy under treatment, recent acute illness requiring hospitalization, or current use of nephrotoxic drugs. Patients with type 1 diabetes, gestational diabetes, and secondary causes of hyperglycemia were also excluded. The final cohort comprised 50 male and 50 female participants, balanced deliberately to permit sex-stratified analyses.

2.3 Biochemical and Hematological Measurements

After an overnight fast of at least eight hours, venous blood (6 mL) was collected from each participant using a standard vacutainer system. EDTA tubes were used for HbA1c estimation and CBC; sodium fluoride tubes were used for fasting plasma glucose; and serum-separator tubes were used for creatinine, urea, and BUN. A spot urine sample was simultaneously collected for ACR determination. HbA1c was measured by immunoturbidimetry on an automated analyser calibrated against the DCCT reference standard. FBS was estimated by the glucose oxidase-peroxidase method. Serum creatinine was measured using the IDMS-traceable kinetic Jaffe method. eGFR was calculated using the 2021 race-free CKD-EPI creatinine equation (Inker et al., 2021). Serum urea was estimated by the urease-glutamate dehydrogenase enzymatic method, and BUN was derived as urea (mg/dL) ÷ 2.14. Urinary albumin was quantified by immunoturbidimetry and urinary creatinine by the Jaffe method, with ACR expressed in mg/g. CBC was performed on a five-part differential automated haematology analyser. Glycemic control categories were defined as: good (HbA1c < 7%), fair (7–7.9%), suboptimal (8–8.9%), and poor (≥ 9%). ACR categories were defined per KDIGO 2024 as normoalbuminuria (< 30 mg/g), microalbuminuria (30–300 mg/g), and macroalbuminuria (> 300 mg/g).

2.4 Statistical Analysis

Statistical analyses were performed using IBM SPSS version 26.0 and the Python scientific stack (NumPy, pandas, SciPy, scikit-learn). Normality was assessed using the Shapiro-Wilk test. Continuous variables are reported as mean ± SD or median (IQR) as appropriate. Group differences were assessed using Student's independent t-test (with Welch's correction) and one-way ANOVA with post-hoc Tukey HSD correction. Bivariate associations were quantified by Pearson correlation. Simple and multiple linear regression models were constructed with log-transformed ACR as the dependent variable. Diagnostic performance of markers for albuminuria (ACR ≥ 30 mg/g) was assessed by ROC curve analysis with Youden-index-identified optimal cut-offs. Statistical significance was set at $p < 0.05$ (two-sided) throughout.

3. RESULTS

3.1 Demographic and Clinical Characteristics

A total of 100 patients with type 2 diabetes mellitus were enrolled. The cohort comprised 50 male and 50 female participants with a mean age of 51.0 ± 15.9 years (range 12–83 years). Patients in the fifth and sixth decades constituted the largest age groups, consistent with the typical presentation of type 2

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ISSN: (e) 3007-1607 (p) 3007-1593

diabetes in the Pakistani population. The mean age was similar between men (50.4 years) and women (51.6 years). Descriptive statistics for the principal biochemical and haematological variables are summarised in Table 1.

Mean HbA1c was 8.14 ± 2.47%, indicating that the cohort was, on average, above the ADA target of 7%, with values ranging from 5.2% to 18.2%. Mean FBS was 172.3 ± 45.0 mg/dL, consistently elevated above the diagnostic threshold of 126 mg/dL. Serum creatinine averaged 1.65 ± 1.05 mg/dL, with a median of 1.20 mg/dL and a maximum of 7.10 mg/dL. The mean eGFR was 58.24 ± 25.82 mL/min/1.73 m², indicating moderately reduced kidney function on average. The urinary ACR showed a right-skewed distribution with a median of 86.5 mg/g and a maximum of 980.7 mg/g. Mean haemoglobin of 11.64 ± 1.29 g/dL fell below the WHO lower limit of normal for both sexes, indicating that mild-to-moderate anaemia was prevalent in this cohort.

Table 1. Descriptive statistics for the principal biochemical and haematological variables (n = 100).

Variable	Mean ± SD	Median	IQR	Range
Age (years)	51.0 ± 15.9	52.0	38.0 – 64.0	12 – 83
FBS (mg/dL)	172.3 ± 45.0	176.0	138.0 – 204.3	40 – 295
HbA1c (%)	8.14 ± 2.47	7.20	6.60 – 8.83	5.2 – 18.2
Serum creatinine (mg/dL)	1.65 ± 1.05	1.20	1.00 – 1.80	0.7 – 7.1
Serum urea (mg/dL)	48.55 ± 32.67	29.00	25.00 – 62.50	19 – 195
BUN (mg/dL)	22.69 ± 15.26	13.60	11.70 – 29.20	8.9 – 91.1
ACR (mg/g)	147.8 ± 184.1	86.5	51.5 – 158.9	12.8 – 980.7
eGFR (mL/min/1.73 m²)	58.24 ± 25.82	61.37	39.69 – 77.16	8.5 – 120.8
Haemoglobin (g/dL)	11.64 ± 1.29	12.15	11.00 – 12.60	7.1 – 13.2
RBC ($\times 10^6$/µL)	4.25 ± 0.42	4.35	4.10 – 4.48	2.85 – 5.06
HCT (%)	37.26 ± 3.72	38.65	35.50 – 40.00	23.8 – 41.8
WBC ($\times 10^3$/µL)	9.05 ± 1.45	8.60	8.00 – 9.80	6.3 – 13.9
Platelets ($\times 10^3$/µL)	265.4 ± 36.6	269.0	247.3 – 285.0	155 – 375

3.2 Glycemic Control: Categories and Distribution

Of the 100 participants, 39 (39.0%) were classified as having good glycemic control (HbA1c < 7%), 28 (28.0%) fair control (7–7.9%), 9 (9.0%) suboptimal control (8–8.9%), and 24 (24.0%) poor control (≥ 9%). Combined, 61 patients (61.0%) had HbA1c ≥ 7% and were classified as having uncontrolled glycemia. The HbA1c distribution was right-skewed with a substantial tail above 10%, reflecting the burden of poorly controlled disease in this clinic-based population. The scatter plot of FBS against HbA1c demonstrated a strong positive linear relationship ($r = +0.718$, $p < 0.001$), confirming the internal consistency of the two glycemic markers.

3.3 Comparison of Renal Markers by Glycemic Control Status

Renal and haematological parameters were compared between controlled (HbA1c < 7%, n = 39) and uncontrolled (HbA1c ≥ 7%, n = 61) groups. Patients with uncontrolled glycemia had significantly higher serum creatinine (1.87 ± 1.23 vs 1.29 ± 0.53 mg/dL; $p = 0.001$), serum urea (56.6 ±

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ISSN: (e) 3007-1607 (p) 3007-1593

36.8 vs 36.0 ± 19.5 mg/dL; p < 0.001), and BUN (26.4 ± 17.2 vs 16.8 ± 9.1 mg/dL; p < 0.001), with significantly lower eGFR (51.5 ± 25.8 vs 68.8 ± 22.3 mL/min/1.73 m²; p < 0.001) and haemoglobin (11.30 ± 1.42 vs 12.17 ± 0.84 g/dL; p < 0.001). Mean ACR was numerically higher in the uncontrolled group (170.2 vs 112.8 mg/g) but did not reach significance (p = 0.097), reflecting within-group variance. Results are presented in Table 2.

Table 2. Comparison of renal and haematological markers between controlled (HbA1c < 7%) and uncontrolled (HbA1c ≥ 7%) glycemia. Values are mean ± SD.

Parameter	Controlled (n=39)	Uncontrolled (n=61)	t-value	p-value
FBS (mg/dL)	140.8 ± 34.2	192.4 ± 39.3	-6.95	< 0.001
Serum creatinine (mg/dL)	1.29 ± 0.53	1.87 ± 1.23	-3.28	0.001
Serum urea (mg/dL)	36.0 ± 19.5	56.6 ± 36.8	-3.63	< 0.001
BUN (mg/dL)	16.8 ± 9.1	26.4 ± 17.2	-3.63	< 0.001
ACR (mg/g)	112.8 ± 135.0	170.2 ± 207.5	-1.68	0.097
eGFR (mL/min/1.73 m²)	68.8 ± 22.3	51.5 ± 25.8	3.57	< 0.001
Haemoglobin (g/dL)	12.17 ± 0.84	11.30 ± 1.42	3.80	< 0.001

One-way ANOVA across the four HbA1c categories revealed a monotonically graded relationship between glycemic burden and renal injury. Significant differences were observed for serum creatinine (F = 3.69, p = 0.015), serum urea (F = 4.58, p = 0.005), BUN (F = 4.57, p = 0.005), eGFR (F = 4.42, p = 0.006), and haemoglobin (F = 5.13, p = 0.002). Mean serum creatinine rose from 1.29 mg/dL in patients with good control to 2.08 mg/dL in those with poor control, while mean eGFR declined from 68.8 to 47.1 mL/min/1.73 m² across the same gradient.

3.4 Albuminuria Prevalence and CKD Staging

Among the 100 participants, 15 (15.0%) had normoalbuminuria (ACR < 30 mg/g), 76 (76.0%) had microalbuminuria (30–300 mg/g), and 9 (9.0%) had macroalbuminuria (> 300 mg/g). The very high prevalence of microalbuminuria reflects the clinic-based sampling frame. Application of the KDIGO 2024 CKD staging to eGFR data revealed that 47% of patients had stage G3 or worse CKD, the majority of whom had not been formally diagnosed at the time of enrolment. The distribution across ACR categories and CKD stages is presented in Table 3.

Table 3. Distribution of patients across ACR categories and CKD stages (KDIGO 2024 classification).

ACR / CKD Category	Definition	n	%
Normoalbuminuria	ACR < 30 mg/g	15	15.0%
Microalbuminuria	30–300 mg/g	76	76.0%
Macroalbuminuria	> 300 mg/g	9	9.0%
CKD G1 (eGFR ≥ 90)	≥ 90 mL/min/1.73 m²	14	14.0%
CKD G2 (eGFR 60–89)	60–89 mL/min/1.73 m²	39	39.0%
CKD G3a (eGFR 45–59)	45–59 mL/min/1.73 m²	15	15.0%
CKD G3b (eGFR 30–44)	30–44 mL/min/1.73 m²	15	15.0%

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ISSN: (e) 3007-1607 (p) 3007-1593

CKD G4 (eGFR 15–29)	15–29 mL/min/1.73 m²	10	10.0%
CKD G5 (eGFR < 15)	< 15 mL/min/1.73 m²	7	7.0%

3.5 Pearson Correlation Analysis

Pearson correlation analysis revealed significant positive correlations between HbA1c and conventional renal markers, and a significant inverse correlation with eGFR and haemoglobin (Table 4). The correlation between HbA1c and ACR did not reach significance (r = +0.037, p = 0.715), most likely because of the skewed distribution of ACR and the compression of the dynamic range in this clinic-based cohort with high baseline microalbuminuria prevalence. The very strong correlations between eGFR and the conventional markers (r = −0.796 to −0.845 for creatinine, urea, and BUN; r = +0.857 for haemoglobin) confirm the expected biological co-variation of these indices once functional impairment is established.

Table 4. Pearson correlation coefficients between HbA1c, eGFR, and selected biochemical markers (n = 100).

Variable Pair	Pearson r	p-value	Interpretation
HbA1c vs Creatinine	+0.292	0.003	Weak-to-moderate positive
HbA1c vs Urea	+0.308	0.002	Weak-to-moderate positive
HbA1c vs BUN	+0.307	0.002	Weak-to-moderate positive
HbA1c vs ACR	+0.037	0.715	Non-significant
HbA1c vs eGFR	-0.288	0.004	Weak-to-moderate negative
HbA1c vs Haemoglobin	-0.358	< 0.001	Moderate negative
HbA1c vs FBS	+0.718	< 0.001	Strong positive
eGFR vs Creatinine	-0.796	< 0.001	Strong negative
eGFR vs Urea	-0.845	< 0.001	Very strong negative
eGFR vs Haemoglobin	+0.857	< 0.001	Very strong positive

3.6 Regression Analysis

Simple linear regression confirmed that HbA1c was a statistically significant predictor of serum creatinine (R^2 = 0.085, p = 0.003), serum urea (R^2 = 0.095, p = 0.002), BUN (R^2 = 0.094, p = 0.002), and eGFR (R^2 = 0.083, p = 0.004). Each 1% increment in HbA1c was associated with a 0.12 mg/dL rise in serum creatinine and a 3.02 mL/min/1.73 m² fall in eGFR. In the multiple linear regression model with log(ACR) as the dependent variable and HbA1c, FBS, serum creatinine, age, and haemoglobin as predictors (adjusted R^2 = 0.048), haemoglobin was the only statistically significant independent predictor (standardised β = −0.364), indicating that lower haemoglobin was the strongest correlate of higher urinary albumin excretion in this cohort.

3.7 Haematological Changes in Relation to Glycemia and Renal Function

Mean haemoglobin of 11.64 ± 1.29 g/dL was below WHO thresholds for both sexes, confirming mild-to-moderate anaemia as a prevalent complication. Haemoglobin declined progressively across HbA1c categories, from 12.17 ± 0.84 g/dL in those with good control to 10.96 ± 1.61 g/dL in those with poor control (ANOVA F = 5.13, p = 0.002). The very strong positive correlation between haemoglobin and eGFR (r = +0.857, p < 0.001) is biologically consistent with the progressive loss of erythropoietin synthesis as nephron mass declines. This strong association was further highlighted by haemoglobin's dominance as the single most

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ISSN: (e) 3007-1607 (p) 3007-1593

influential predictor of urinary ACR in the multivariable regression model.

3.8 Diagnostic Performance of Glycemic and Renal Markers

ROC curve analysis for the prediction of albuminuria (ACR ≥ 30 mg/g) demonstrated that HbA1c had the highest area under the curve (AUC = 0.723), followed by FBS (AUC = 0.673), and serum creatinine, urea and BUN (AUC = 0.662 each). The optimal HbA1c cut-off of 7.20%, determined by maximising the Youden index, yielded a sensitivity of 60% and specificity of 87%. Notably, this threshold is essentially identical to the ADA target for HbA1c, supporting its use as the clinical decision point for intensifying glycemic management to reduce incipient nephropathy risk (American Diabetes Association, 2023). Detailed ROC statistics are provided in Table 5.

Table 5. Receiver operating characteristic analysis for the prediction of albuminuria (ACR ≥ 30 mg/g; n = 100).

Marker	AUC	Optimal Cut-off	Sensitivity	Specificity
HbA1c (%)	0.723	7.20%	60%	87%
FBS (mg/dL)	0.673	143 mg/dL	79%	53%
Serum creatinine (mg/dL)	0.662	1.40 mg/dL	48%	87%
Serum urea (mg/dL)	0.662	52.5 mg/dL	48%	87%
BUN (mg/dL)	0.662	24.5 mg/dL	48%	87%

4. DISCUSSION

4.1 Burden of Poor Glycemic Control and Renal Risk

The most striking finding of the present study is that 61% of patients attending the diabetic outpatient clinic in Faisalabad had HbA1c values at or above the ADA target of 7%, with one quarter having HbA1c ≥ 9%, indicating a very substantial burden of poorly controlled disease. This proportion is consistent with published estimates from across South Asia, where the mean HbA1c of patients in diabetic clinics exceeds international targets by one to two percentage points, and structural barriers to medication adherence, dietary modification, and self-monitoring of blood glucose remain pervasive (Hussain et al., 2023; Aamir et al., 2025). The downstream consequences for renal function were evident across every comparison performed: serum creatinine, urea, and BUN were all significantly higher, and eGFR significantly lower, in patients with HbA1c ≥ 7%. The graded, monotonic relationship between HbA1c categories and renal biochemistry is particularly compelling evidence of a dose-response relationship between cumulative glycemic exposure and renal injury.

These findings are consistent with the landmark DCCT/EDIC and UKPDS trials, which demonstrated that intensive glycemic control substantially reduced microvascular endpoints including nephropathy in both type 1 and type 2 diabetes (DCCT/EDIC Research Group, 2003; UK Prospective Diabetes Study Group, 1998), and with the combined PERL/ACCORD analysis which showed that higher HbA1c was significantly associated with faster eGFR decline in patients with established DKD (Shah et al., 2024). Regional studies from Pakistan have reported comparable proportions of uncontrolled glycemia, and similar associations between HbA1c and renal markers, underscoring the universality of this relationship and the need for region-specific implementation of international screening recommendations (Waheed et al., 2014; Aamir et al., 2025; Qamar et al., 2025).

4.2 Mechanistic Basis of the Observed Associations

The molecular pathway from sustained hyperglycemia to diabetic kidney disease is now well-characterized. Chronic glucose elevation drives AGE formation through non-enzymatic glycation of

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ISSN: (e) 3007-1607 (p) 3007-1593

structural proteins; AGE-RAGE engagement on glomerular endothelial and mesangial cells activates NF-κB and promotes transcription of TNF-α, IL-6, and TGF-β, which collectively amplify oxidative injury, recruit macrophage infiltrates, and drive fibrotic remodeling of the mesangial matrix (Donath & Shoelson, 2011; Alicic et al., 2022). Simultaneously, polyol and hexosamine pathway flux depletes NADPH and glutathione, generating reactive oxygen species that damage mitochondria and disrupt tubular epithelial cell homeostasis. At the podocyte level, hyperglycemia disrupts actin cytoskeletal architecture and slit-diaphragm proteins, resulting in increased albumin leak through the glomerular filtration barrier (Thomas et al., 2023). The elevated serum creatinine, urea, and BUN observed in our uncontrolled group represent the biochemical signature of this cumulative structural damage.

4.3 HbA1c as a Diagnostic Marker for Incipient Nephropathy

HbA1c emerged as the strongest discriminator of albuminuria in this cohort, with an AUC of 0.723 and an optimal cut-off of 7.20%. This finding aligns with a substantial body of literature. Kundu et al. reported that HbA1c correlated significantly with ACR, eGFR, and serum creatinine in type 2 diabetes (Kundu et al., 2017). Gupta and Rawal confirmed that the combination of HbA1c and ACR provided the most clinically meaningful prediction of early renal involvement in type 2 diabetic patients attending a tertiary care hospital (Gupta & Rawal, 2023). Idowu et al. demonstrated by multivariate analysis that HbA1c was an independent predictor of albuminuria, even after accounting for diabetes duration and lipid ratios (Idowu et al., 2017). The observation that the optimal cut-off in our cohort sits at 7.2%, essentially identical to the ADA action threshold, provides direct pragmatic support for incorporating HbA1c-triggered albuminuria screening into routine diabetic clinic practice without requiring a separate decision algorithm.

The more modest correlation between HbA1c and raw ACR ($r = +0.037$, $p = 0.715$) compared with eGFR-based markers warrants careful interpretation. Several factors explain this apparent paradox. First, 76% of the cohort already had microalbuminuria at enrolment, compressing the dynamic range of the ACR measurement and attenuating the correlation signal. Second, spot ACR is influenced by transient physiological perturbations including exercise, acute hyperglycemic excursions, fever, and posture changes (Afkarian et al., 2020). Third, an emerging body of evidence recognizes that a substantial minority of patients with DKD progress to ESRD through non-proteinuric pathways, exhibiting a declining eGFR without antecedent macroalbuminuria, particularly in elderly patients and women (Astor et al., 2002; Tuttle et al., 2021). These considerations reinforce the current consensus that ACR and eGFR should be measured and interpreted together, and that neither alone is sufficient for comprehensive risk stratification.

4.4 Significance of Haematological Findings

The finding that haemoglobin was the strongest independent predictor of urinary ACR in multivariable regression (standardised $\beta = -0.364$) was an important observation not originally anticipated as the primary outcome. The biological interpretation is straightforward: as eGFR declines, peritubular fibroblast loss reduces erythropoietin synthesis; concurrent uremic inflammation elevates hepcidin, sequestering iron; and uremic toxins suppress bone marrow erythropoiesis and shorten erythrocyte lifespan, resulting in normocytic anaemia that tracks closely with the severity of renal functional impairment (Lee et al., 2021; KDIGO Anemia Work Group, 2012). The very strong haemoglobin-eGFR correlation ($r = +0.857$) seen in this cohort provides striking epidemiological confirmation of this mechanism.

Beyond its mechanistic interest, this finding has direct clinical implications. Haemoglobin is routinely measured as part of the CBC in every diabetic patient at every clinic visit, at negligible additional cost. A falling haemoglobin in a diabetic patient should therefore prompt urgent assessment of eGFR and ACR, even in the absence of symptoms. This is particularly relevant in Pakistani clinical settings, where the transition from normo-albuminuria to microalbuminuria may occur asymptomatically, and where dedicated renal monitoring is inconsistently performed (Aamir et al., 2025; Areej et al., 2025). The practical

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ISSN: (e) 3007-1607 (p) 3007-1593

recommendation arising from the present data is that haemoglobin should be considered as an early sentinel biomarker of diabetic renal dysfunction and incorporated into clinical decision-making alongside HbA1c, ACR, and eGFR.

4.5 Clinical Implications

The present findings carry several actionable implications for the management of type 2 diabetes in primary and secondary care. First, HbA1c should be measured at every diabetic clinic visit and its value used directly to trigger intensification of glycemic management (target < 7%) and renal screening (ACR and eGFR) simultaneously, since an HbA1c ≥ 7.2% in this cohort had 60% sensitivity and 87% specificity for the presence of albuminuria. Second, urinary ACR and eGFR should be measured together as a combined panel at every annual review for all patients with diabetes, regardless of disease duration, because 47% of patients in this clinic-based cohort had stage G3 or worse CKD, yet most were not formally diagnosed (KDIGO Diabetes Work Group, 2020). Third, haemoglobin should be monitored as a supplementary biomarker of renal health, not merely of anemia, given its strong association with eGFR and its role as an independent predictor of urinary albumin excretion. Fourth, where available, the addition of SGLT2 inhibitors and renin-angiotensin-system blockade should be considered early in patients with ACR ≥ 30 mg/g, since these agents have demonstrated renoprotective benefits independent of their blood glucose and blood pressure lowering effects (Tuttle et al., 2021; KDIGO Diabetes Work Group, 2020).

4.6 Study Strengths and Limitations

The principal strengths of this study include the balanced sex composition of the cohort, the integration of glycemic, renal, and haematological data from the same individuals at the same visit, the use of the 2021 race-free CKD-EPI equation and KDIGO 2024 albuminuria and CKD classifications, and the application of a coherent analytical framework progressing from descriptive statistics through bivariate correlation, regression, and diagnostic ROC analysis. The use of standardised laboratory platforms with internationally traceable calibrators further strengthens the reliability of the measurements.

Limitations include the cross-sectional design, which precludes causal inference and cannot capture the temporal dynamics of incipient nephropathy. The sample of 100 patients limits power to detect smaller effects and to perform meaningful sub-group analyses. Reliance on a single spot ACR measurement may have overestimated the true prevalence of microalbuminuria. Novel markers such as cystatin C, NGAL, and KIM-1, as well as ambulatory blood pressure measurements, were not available and would have enriched the early-injury assessment. Finally, the clinic-based sample from a single centre limits generalizability to community populations and to other regions of Pakistan.

5. CONCLUSION

This cross-sectional study of 100 patients with type 2 diabetes mellitus attending a tertiary care clinic in Faisalabad, Pakistan demonstrates that poor glycemic control, defined by HbA1c ≥ 7%, is strongly and consistently associated with early biochemical markers of kidney dysfunction including elevated serum creatinine, urea, and BUN, reduced eGFR, and a high prevalence of microalbuminuria. HbA1c outperformed fasting blood sugar, serum creatinine, urea, and BUN in predicting albuminuria, with an optimal cut-off of 7.2% that coincides precisely with the internationally endorsed ADA treatment target. Haemoglobin emerged as the dominant independent predictor of urinary albumin excretion in multivariable analysis, reflecting the early onset of anemia of renal origin in the natural history of diabetic kidney disease.

These findings support an integrated clinical monitoring framework in which HbA1c, urinary ACR, eGFR, and haemoglobin are routinely assessed together at every annual review of the diabetic patient. Implementation of this framework in Pakistani primary and secondary care settings would facilitate earlier identification of incipient nephropathy, allow timely initiation of renoprotective therapies, and reduce the progression to ESRD in this high-risk population. Future longitudinal studies with larger sample sizes, multiple ACR measurements, and novel biomarker

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panels are warranted to validate and extend these findings.

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