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Clinical profile of non-proteinuric kidney disease in Type 2 diabetic patients.

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ABSTRACT… Objective: To compare the demographic, clinical, and biochemical characteristics of nonproteinuric versus proteinuric diabetic kidney disease (DKD) among patients with type 2 diabetes mellitus (T2DM). **Study Design:** Cross-sectional Observational study. **Setting:** Department of Nephrology, Nishtar Hospital, Multan. **Period:** November 2024 to April 2025. **Methods:** Adult patients diagnosed with T2DM attending the Nephrology Department of Nishtar Hospital, Multan, were enrolled through non-probability consecutive sampling based on predefined inclusion criteria. Participants were classified into nonproteinuric and proteinuric DKD groups according to standard albuminuria cut-offs and estimated glomerular filtration rate (eGFR) values. Baseline demographic details, clinical data, and biochemical profiles were systematically documented and compared between both groups using appropriate statistical tests. A p-value < 0.05 was considered statistically significant. **Results:** Among 300 patients, nonproteinuric diabetic kidney disease (DKD) was observed in 32.3%. Compared to the proteinuric group, nonproteinuric DKD had mean age (55.33 ± 7.99 vs 58.67 ± 7.43 years, $p < 0.001$), shorter diabetes duration (10.75 ± 3.65 vs 12.80 ± 4.25 years), higher hemoglobin (11.27 ± 1.05 vs 10.35 ± 1.61 g/dL), higher serum albumin (3.87 ± 0.62 vs 3.42 ± 0.31 g/dL), lower serum creatinine (1.15 ± 0.26 vs 1.42 ± 0.39 mg/dL, $p < 0.001$), lower HbA1c (7.02 ± 1.15% vs 7.71 ± 1.31%), and higher eGFR (54.90 ± 13.17 vs 41.94 ± 8.21 ml/min/1.73m^2). Hypertension, dyslipidemia, and RAAS inhibitor use were more frequent in the proteinuric group (all $p < 0.05$). **Conclusion:** Nonproteinuric diabetic kidney disease is common in type 2 diabetes and exhibits distinct demographic and biochemical features compared to proteinuric DKD, underscoring the need for targeted recognition and management.

Key words: Diabetic Kidney Disease, Nonproteinuric DKD, Proteinuric DKD, Renal Function, T2DM.

INTRODUCTION

Diabetic kidney disease (DKD) remains the most common microvascular complication of diabetes mellitus and is a major contributor of chronic kidney disease and end-stage renal disease (ESRD) worldwide.[1] Traditionally, DKD has been characterized by a progression from normoalbuminuria to microalbuminuria, followed by overt proteinuria and a decrease in renal function.[2] Proteinuria, especially in the form of albuminuria, has long been regarded as the primary clinical marker and prognostic indicator of DKD. This paradigm, however, is increasingly being challenged by reports that a notable subset of T2DM patients develop significant renal impairment in absence of overt proteinuria.[3,4]is a major cause of end-stage kidney disease (ESKD Recent epidemiological studies across diverse populations have identified nonproteinuric or nonalbuminuric DKD as a clinically relevant phenotype, with prevalence estimates ranging from 8% to over 45% among individuals with T2DM and CKD.[5,6]inflammation, bone disease, and disturbance in endocrine function. Unlike in the management of patients with predialysis CKD, bicarbonate levels were not being routinely monitored in dialysis patients at our center. The KDOQI guidelines recommend serum bicarbonate levels ≥22 mEq/L in patients on dialysis. We measured the predialysis serum bicarbonate levels in 100 adult patients on regular hemodialysis (HD A large Chinese cohort found that approximately 9% of biopsy-confirmed DKD cases were nonproteinuric, whereas hospital- and population-based studies in India and Europe reported much higher proportions, up to 47% in

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certain outpatient cohorts.[6,7]

The underlying mechanisms responsible for the development of nonproteinuric DKD remain incompletely understood. Histopathological and clinical analyses suggest that these patients often exhibit less severe glomerular injury but greater vascular and tubulointerstitial involvement, with macroangiopathic changes and preserved tubular albumin reabsorption thought to play important roles.[8,9]contributing to chronic renal disease. Objective: To determine the frequency of diabetic nephropathy and its correlation with glycemic control. Methods: A cross-sectional study was conducted at the Nephrology and Diabetic OPD of Lahore General Hospital from July to November 2024. A total of 282 type 2 diabetic patients were enrolled. Clinical evaluation, fundoscopy, neurological examination, and laboratory tests were performed. Diabetic nephropathy was diagnosed based on albuminuria and eGFR. Statistical significance was set at $p < 0.05$. Results: Out of 282 patients, 150 (53.2% Yamanouchi et al., have identified older age, absence of diabetic retinopathy, higher hemoglobin, and better glycemic control as factors more frequently associated with the nonproteinuric DKD.[10] In addition, the extensive utilization of renin-angiotensin system inhibitors and newer glucose-lowering agents may contribute to lower albumin excretion, further complicating the classical diagnostic approach.[11] Jasmine Sethi et al. reported that nonproteinuric DKD is linked with a slower decrease in eGFR and a lower risk of progression to ESRD, though others find comparable rates of renal function loss to proteinuric forms, particularly over extended follow-up.[12] Macrovascular complications, including cardiovascular and cerebrovascular events, are also more common in the nonproteinuric group, suggesting distinct pathophysiological pathways and prognostic implications.[13]

Despite growing recognition, nonproteinuric DKD remains under characterized in many populations, and standard screening practices focused on proteinuria may overlook a notable number of affected individuals. As a result, there are important gaps in knowledge regarding the clinical features, risk factors, and progression patterns of nonproteinuric DKD, especially within South Asian cohorts. This study aims to determine whether nonproteinuric DKD in type 2 diabetic patients exhibits distinct demographic, clinical, and laboratory features compared to proteinuric phenotype.

METHODS

A cross-sectional study was executed in Department of Nephrology at Nishtar Hospital, Multan, spanning November 2024 to April 2025. The research received approval from Ethical Review Board of Nishtar Medical University, Multan (18964/NMU), and all patients provided written informed consent prior to enrollment. Participants were recruited using a non-probability consecutive sampling approach. The required sample size of 300 was estimated using the WHO calculator, with the calculation based on an anticipated prevalence of 26.5% for nonproteinuric DKD among individuals with T2DM, a confidence level of 95%, and a 5% margin of error.[5]inflammation, bone disease, and disturbance in endocrine function. Unlike in the management of patients with predialysis CKD, bicarbonate levels were not being routinely monitored in dialysis patients at our center. The KDOQI guidelines recommend serum bicarbonate levels ≥22 mEq/L in patients on dialysis. We measured the predialysis serum bicarbonate levels in 100 adult patients on regular hemodialysis (HD

Patients aged 18 years or above of either sex, diagnosed with T2DM and presenting with either proteinuria exceeding 500 mg per day or reduced renal function (eGFR less than 60 mL/min/1.73 m^2), with a minimum diabetes duration of one year, were eligible for inclusion. Exclusion criteria encompassed those with type 1 diabetes, recent acute kidney injury (within the last three months), primary glomerular or polycystic kidney disorders, autoimmune conditions, malignancy, current need for renal replacement therapy, or any alternative cause of proteinuria or impaired renal function unrelated to diabetes.

A proforma was used to gather the baseline

information, including age, sex, duration of diabetes, BMI and comorbidities such as hypertension, dyslipidemia, smoking status and history of cardiovascular disease and cerebrovascular accidents. Diagnosis of diabetic retinopathy was established based on ophthalmological examination findings, and diabetic neuropathy was determined through clinical neurological evaluation. Medication history, including the use of RAAS inhibitors, and dapagliflozin, was documented. Laboratory investigations were carried out in the institutional laboratory using standardized methods. Blood samples were taken for serum creatinine, hemoglobin, glycated hemoglobin (HbA1c), and serum albumin. The eGFR was calculated using the CKD-EPI equation. Urine sample was collected to check for UACR, which was measured by immunoturbidimetric assay. Patients with UACR ≥ 30mg/g or documented 24-hour urinary protein >500 mg/day were classified as having proteinuric DKD, whereas those with UACR <30 mg/g and proteinuria <500 mg/day, despite an eGFR <60 mL/min/1.73 m^2, were categorized as nonproteinuric DKD (NP-DKD). Data completeness was ensured by immediate review of forms; participants with missing core variables were excluded from the final analysis.

Data were analyzed using SPSS version 26.0. Means and standard deviations were calculated for numerical variables, which were compared between groups using independent t-tests. Grouped variables were summarized as numbers and percentages and analyzed by chi-square test. Multivariable logistic regression was performed to identify independent predictors of the nonproteinuric diabetic kidney disease phenotype. A p-value below 0.05 was considered statistically significant.

RESULTS

Among 300 patients, nonproteinuric DKD was observed in 97 (32.3%), while 203 (67.7%) had proteinuric diabetic kidney disease (Figure-1).

Patients with nonproteinuric DKD were younger (55.33 ± 7.99 vs 58.67 ± 7.43 years) and had a shorter diabetes duration (10.75 ± 3.65 vs 12.80 ± 4.25 years, p < 0.001) than those with proteinuric DKD. The nonproteinuric patients had lower prevalence of hypertension (67.0% vs 79.8%, p = 0.016), dyslipidemia (47.4% vs 61.1%, p = 0.026), diabetic retinopathy (37.1% vs 61.1%), diabetic neuropathy (25.8% vs 39.4%, p = 0.021), and RAAS inhibitor use (40.2% vs 66.5%, p < 0.001) compared to the proteinuric patients (Table-I).

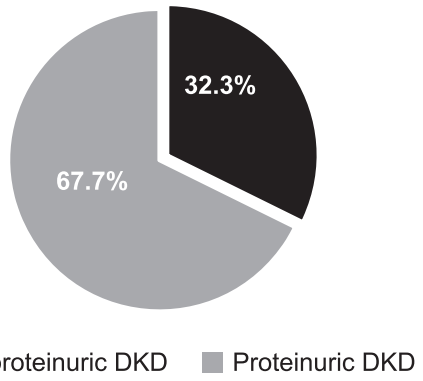

Figure-1. Diabetic kidney disease phenotype distribution

The nonproteinuric DKD group had significantly higher hemoglobin (11.27 ± 1.05 vs 10.35 ± 1.61 g/dL), higher S/albumin (3.87 ± 0.62 vs 3.42 ± 0.31 g/dL), lower glycated hemoglobin (7.02 ± 1.15% vs 7.71 ± 1.31%), lower S/creatinine (1.15 ± 0.26 vs 1.42 ± 0.39 mg/dL), and higher eGFR (54.90 ± 13.17 vs 41.94 ± 8.21 ml/min/1.73m^2) compared to proteinuric DKD group. UACR was markedly lower in nonproteinuric group (27.68 ± 34.46 vs 450.89 ± 102.22 mg/g) (Table-II).

On multivariable logistic regression, increasing age (OR 0.878, 95% CI 0.816–0.946, p = 0.001), longer duration of diabetes (OR 0.861, 95% CI 0.756–0.981, p = 0.024), higher serum creatinine (OR 0.028, 95% CI 0.002–0.319, p = 0.004), and higher glycated hemoglobin (OR 0.327, 95% CI 0.188–0.570, p < 0.001) were linked with reduced odds of nonproteinuric DKD. The presence of hypertension (OR 4.357, 95% CI 1.446–13.128, p = 0.009), dyslipidemia (OR 3.887, 95% CI 1.433–10.543, p = 0.008), RAAS inhibitor use (OR 3.180, 95% CI 1.114–9.078, p = 0.031), higher serum albumin (OR 5.668, 95% CI 1.616–19.881,

p = 0.007), higher hemoglobin (OR 1.939, 95% CI 1.332–2.822, p = 0.001), and higher estimated GFR (OR 1.143, 95% CI 1.085–1.205, p < 0.001) were linked with greater odds of nonproteinuric DKD (Table-III).

DISCUSSION

This study provides a thorough assessment of clinical and biochemical factors distinguishing nonproteinuric from proteinuric DKD among adults with T2DM. The observed frequency of nonproteinuric DKD in this cohort was 32.3%, a figure that aligns with the growing body of global evidence recognizing this phenotype as both common and clinically meaningful. Shi et al., through meta-analysis of 31 studies, reported a combined frequency of nonalbuminuric DKD at 24.7% among DKD patients (95% CI: 17.3–33.7), and 45.6% among those with renal insufficiency.[14]the classical phenotype of DKD, which is characterized by albuminuria preceding renal insufficiency, has been challenged since a subset of diabetic patients with renal insufficiency but without albuminuria has been increasingly reported. However, the available evidence is inconsistent. Thus, the present systematic review will assess and summarize the available data regarding nonalbuminuric diabetic kidney disease (NADKD Other reports show some variability, such as Laranjinha et al., who documented a 46.6% frequency, and Sangha et al., who found a rate of 26.5%.[5,7]inflammation, bone disease, and disturbance in endocrine function. Unlike in the management of patients with predialysis CKD, bicarbonate levels were not being routinely monitored in dialysis patients at our center.

Variable	Category	Nonproteinuric DKD	Proteinuric DKD	χ^2 / t-value	P-Value
Age (years)	Mean ± SD	55.33 ± 7.99	58.67 ± 7.43	t = -3.554	<0.001
Diabetes Duration (years)	Mean ± SD	10.75 ± 3.65	12.80 ± 4.25	t = -4.086	<0.001
BMI (kg/m^2)	Mean ± SD	27.35 ± 3.51	28.13 ± 3.36	t = -1.863	0.063
Gender	Male, n (%)	51 (52.6%)	120 (59.1%)	χ^2 = 1.144	0.285
	Female, n (%)	46 (47.4%)	83 (40.9%)		
Hypertension	Yes, n (%)	65 (67.0%)	162 (79.8%)	χ^2 = 5.834	0.016
Dyslipidemia	Yes, n (%)	46 (47.4%)	124 (61.1%)	χ^2 = 4.988	0.026
History of Cardiovascular disease	Yes, n (%)	21 (21.6%)	54 (26.6%)	χ^2 = 0.858	0.354
History of Cerebrovascular accident	Yes, n (%)	6 (6.2%)	15 (7.4%)	χ^2 = 0.146	0.702
Smoking	Yes, n (%)	24 (24.7%)	54 (26.6%)	χ^2 = 0.118	0.731
Diabetic retinopathy	Yes, n (%)	36 (37.1%)	124 (61.1%)	χ^2 = 15.153	<0.001
Diabetic neuropathy	Yes, n (%)	25 (25.8%)	80 (39.4%)	χ^2 = 5.364	0.021
RAAS inhibitor use (ACEI/ARB)	Yes, n (%)	39 (40.2%)	135 (66.5%)	χ^2 = 18.632	<0.001
Dapagliflozin use	Yes, n (%)	21 (21.6%)	39 (19.2%)	χ^2 = 0.244	0.621

Table-I. Baseline characteristics of study participants with diabetic kidney disease

Variable	Nonproteinuric DKD (Mean ± SD)	Proteinuric DKD (Mean ± SD)	P-Value
Hemoglobin (g/dL)	11.27 ± 1.05	10.35 ± 1.61	<0.001
Glycated hemoglobin (%)	7.02 ± 1.15	7.71 ± 1.31	<0.001
Serum creatinine (mg/dL)	1.15 ± 0.26	1.42 ± 0.39	<0.001
Serum albumin (g/dL)	3.87 ± 0.62	3.42 ± 0.31	<0.001
eGFR (ml/min/1.73m^2)	54.90 ± 13.17	41.94 ± 8.21	<0.001
UACR (mg/g)	27.68 ± 34.46	450.89 ± 102.22	<0.001

Table-II. Comparison of biochemical parameters between nonproteinuric and proteinuric diabetic kidney disease groups

Variable	Odds Ratio (OR)	95% Confidence Interval	P-Value
Age (years)	0.878	0.816 – 0.946	0.001
Duration of diabetes (years)	0.861	0.756 – 0.981	0.024
BMI (kg/m^2)	1.055	0.912 – 1.221	0.473
Hypertension	4.357	1.446 – 13.128	0.009
Dyslipidemia	3.887	1.433 – 10.543	0.008
Diabetic retinopathy	1.155	0.434 – 3.078	0.773
Diabetic neuropathy	1.299	0.485 – 3.479	0.603
RAAS inhibitor use (ACEI/ARB)	3.180	1.114 – 9.078	0.031
Serum creatinine (mg/dL)	0.028	0.002 – 0.319	0.004
Glycated hemoglobin (%)	0.327	0.188 – 0.570	<0.001
eGFR (ml/min/1.73m^2)	1.143	1.085 – 1.205	<0.001
Serum albumin (g/dL)	5.668	1.616 – 19.881	0.007
Hemoglobin (g/dL)	1.939	1.332 – 2.822	0.001

Table-III. Multivariable logistic regression analysis for predictors of nonproteinuric diabetic kidney disease

The KDOQI guidelines recommend serum bicarbonate levels ≥22 mEq/L in patients on dialysis. We measured the predialysis serum bicarbonate levels in 100 adult patients on regular hemodialysis (HD These variations notwithstanding, the data firmly establish nonproteinuric DKD as a prevalent clinical entity, warranting careful recognition in both clinical practice and future research. Patient age showed a modest but slightly difference between phenotypes, with those in the nonproteinuric DKD group being on average (55.33 ± 7.99 years) compared to the proteinuric DKD group (58.67 ± 7.43 years; $p < 0.001$). While this finding is partly congruent with some prior studies, such as Shi et al., observed nonproteinuric DKD patients to be slightly older (mean difference 1.04 years, 95% CI: 0.52–1.57).[14]the classical phenotype of DKD, which is characterized by albuminuria preceding renal insufficiency, has been challenged since a subset of diabetic patients with renal insufficiency but without albuminuria has been increasingly reported. However, the available evidence is inconsistent. Thus, the present systematic review will assess and summarize the available data regarding nonalbuminuric diabetic kidney disease (NADKD Dai et al. identified age as an independent predictor for nonproteinuric DKD (OR 1.089, 95% CI: 1.055–1.123, $p < 0.001$).[6] Such discrepancies likely reflect underlying differences in patient selection, comorbidity patterns, and the application of diagnostic thresholds across different populations.

With respect to gender and BMI, the current analysis did not identify statistically significant differences between groups (BMI: $p = 0.063$; male gender: $p = 0.285$). These results are parallel with the findings of Laranjinha et al. observed similar distributions of BMI and gender.[7] In this study, patients with nonproteinuric DKD had a shorter duration of diabetes (10.75 ± 3.65 years) than those with proteinuric DKD (12.80 ± 4.25 years). Multivariable analysis confirmed longer duration of diabetes as linked with lower odds of nonproteinuric DKD (OR 0.861, 95% CI: 0.756–0.981, $p = 0.024$). This observation is robustly supported in literature such as Shi et al. documented a mean difference of –2.9 years (95% CI: –3.63 to –2.18) between nonproteinuric and proteinuric DKD.[14]the classical phenotype of DKD, which is characterized by albuminuria preceding renal insufficiency, has been challenged since a subset of diabetic patients with renal insufficiency but without albuminuria has been increasingly reported. However, the available evidence is inconsistent. Thus, the present systematic review will assess and summarize the available data regarding nonalbuminuric diabetic kidney disease (NADKD Nayak and Satpathy, as well as Prasad et al., also reported that shorter diabetes duration characterized nonproteinuric phenotypes,

highlighting the critical role of prompt diagnosis and intervention.[15,16]

Hypertension was less common among patients with nonproteinuric DKD (67.0%) than those with proteinuric DKD (79.8%, p = 0.016), yet paradoxically, hypertension emerged as an independent predictor of the nonproteinuric phenotype in this analysis (OR 4.357, 95% CI: 1.446–13.128, p = 0.009). This result highlights the complex relationship between blood pressure regulation, renal injury pathways, and albuminuria. Yamanouchi et al. found that lower blood pressure (OR 0.95, 95% CI: 0.93–0.97, p < 0.001) predicted the nonproteinuric phenotype, whereas Arora et al. observed a higher prevalence of hypertension among nonproteinuric patients.[10,17] Such variability reflects heterogeneity in underlying pathophysiology, possibly including differences in vascular stiffness, endothelial function, and the impact of antihypertensive therapy.

Dyslipidemia was less prevalent in nonproteinuric DKD (47.4% vs. 61.1%, p = 0.026), yet multivariable analysis indicated that dyslipidemia was associated with nonproteinuric DKD (OR 3.887, 95% CI: 1.433–10.543, p = 0.008). These findings echo those of Robles et al., who noted a higher frequency of dyslipidemia among diabetic patients.[18] Microvascular complications, particularly diabetic retinopathy and neuropathy, were less observed in nonproteinuric DKD (retinopathy: 37.1% vs. 61.1%; neuropathy: 25.8% vs. 39.4%, p = 0.021). Shi et al. reported a relative risk of retinopathy of 0.58 (95% CI: 0.51–0.67) for nonproteinuric compared to proteinuric DKD, and Sangha et al. noted that absence of retinopathy and higher hemoglobin independently predicted nonproteinuric status.[5,14]the classical phenotype of DKD, which is characterized by albuminuria preceding renal insufficiency, has been challenged since a subset of diabetic patients with renal insufficiency but without albuminuria has been increasingly reported. However, the available evidence is inconsistent. Thus, the present systematic review will assess and summarize the available data regarding nonalbuminuric diabetic kidney disease (NADKD Collectively, these results reinforce the notion that nonproteinuric DKD is less frequently complicated by classic microvascular sequelae, supporting the hypothesis that its underlying pathogenesis may be more closely linked to vascular and interstitial mechanisms rather than glomerular injury alone.

Biochemical distinctions in this study further delineate the nonproteinuric DKD phenotype. Patients exhibited higher hemoglobin (11.27 ± 1.05 vs. 10.35 ± 1.61 g/dL), higher serum albumin (3.87 ± 0.62 vs. 3.42 ± 0.31 g/dL), lower serum creatinine (1.15 ± 0.26 vs. 1.42 ± 0.39 mg/dL), higher eGFR (54.90 ± 13.17 vs. 41.94 ± 8.21 ml/min/1.73m^2), and better glycemic control (HbA1c 7.02 ± 1.15% vs. 7.71 ± 1.31%) compared to proteinuric DKD. The UACR was substantially lower (27.68 ± 34.46 vs. 450.89 ± 102.22 mg/g). These observations are parallel with findings from Chang et al., who reported higher serum albumin (41.1 ± 3.6 vs. 32.7 ± 5.8 g/L), higher hemoglobin (12.4 ± 1.8 vs. 11.2 ± 2.0 g/dL), and higher eGFR in nonproteinuric DKD.[19]diabetic nephropathy (DN Nayak and Satpathy described higher baseline eGFR (62.4 ± 8.7 vs. 45.8 ± 12.6 ml/min/1.73m^2) and a slower annual eGFR decline in nonproteinuric DKD.[15] Shi et al., in meta-analysis, confirmed higher hemoglobin and lower HbA1c in nonproteinuric DKD.[14]the classical phenotype of DKD, which is characterized by albuminuria preceding renal insufficiency, has been challenged since a subset of diabetic patients with renal insufficiency but without albuminuria has been increasingly reported. However, the available evidence is inconsistent. Thus, the present systematic review will assess and summarize the available data regarding nonalbuminuric diabetic kidney disease (NADKD RAAS inhibitor use was less frequent in the nonprotei0nuric group (40.2% vs. 66.5%, p < 0.001), yet linked with increased odds of nonproteinuric DKD. The present findings are consistent with recent large-scale studies and meta-analyses demonstrating that nonproteinuric DKD exhibits slower renal function decline, milder histopathological lesions, and lower risk of ESRD and mortality.[14,20]the development of overt proteinuria mark the initiation of GFR decline. However, in the last few years growing evidence has shown that a significant proportion of T2DM

patients has decreased GFR without albuminuria. The present study was done to understand the clinical phenotype of non proteinuric kidney disease in T2DM patients and to compare the progression of CKD between proteinuric and non proteinuric phenotype. Method(s

This study's strengths include a robust sample size, detailed phenotypic characterization, and comprehensive statistical analysis, enabling clear delineation between nonproteinuric and proteinuric DKD. Limitations include its single-center, cross-sectional design, absence of renal histopathology, and lack of longitudinal follow-up, which may affect causal inference and external generalizability. Future research should focus on prospective, multicenter studies with extended follow-up and, where feasible, histopathological correlation, to clarify the underlying mechanisms and long-term outcomes of nonproteinuric DKD and inform targeted management strategies in diverse diabetic populations.

CONCLUSION

This study demonstrates that nonproteinuric diabetic kidney disease constitutes a substantial proportion of DKD in type 2 diabetes, with a frequency of 32.3%. Nonproteinuric DKD is associated with shorter diabetes duration, better glycemic control, higher hemoglobin, higher serum albumin, preserved renal function, and fewer microvascular complications compared to proteinuric DKD. Independent predictors include hypertension, dyslipidemia, RAAS inhibitor use, and higher serum albumin and hemoglobin. These findings highlight the distinct clinical and biochemical profile of nonproteinuric DKD.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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4	**Muhammad Irfan Jamil:** Concept, design, results, discussion.
5	**Anjum Shahzad:** Critical analysis, final approval,
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