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Original Research Article

Non-Proteinuric Kidney Disease in Type 2 Diabetic Patients: Clinical Insights from India

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Abstract:

Background: Diabetic kidney disease (DKD) is a leading cause of end-stage renal disease worldwide, characterized by proteinuria and declining renal function. However, a subset of type 2 diabetic patients presents with a nonproteinuric phenotype, posing diagnostic and management challenges. The study objective was to evaluate the clinical spectrum of nonproteinuric kidney disease in individuals with type 2 diabetes (T2D), offering management implications and insights into the illness's features.

Methods: A single-center, prospective cohort study involving 115 T2D patients was conducted. Participants were categorized into proteinuric and nonproteinuric groups based on predefined criteria. Demographic, clinical, and biochemical parameters were assessed, and logistic regression analysis was performed to identify predictors of the nonproteinuric phenotype.

Results: The study revealed significant variations between proteinuric and nonproteinuric groups in terms of age, BMI, blood pressure, serum creatinine, eGFR, and prevalence of diabetic retinopathy. Logistic regression analysis identified baseline proteinuria (OR 0.25, 95% CI 0.12 - 0.54), systolic blood pressure (OR 1.08, 95% CI 1.02 - 1.15), and duration of diabetes (OR 0.85, 95% CI 0.72 - 0.99) as independent predictors of the nonproteinuric phenotype.

Conclusion: The study highlights the diverse clinical manifestations of DKD in T2D patients and underscores the importance of recognizing the nonproteinuric phenotype. Early identification of predictors such as baseline proteinuria, blood pressure, and duration of diabetes can aid in risk stratification and personalized management strategies to mitigate renal dysfunction progression.

Recommendations: Clinicians should consider assessing for nonproteinuric DKD in T2D patients, particularly those with lower baseline proteinuria, higher systolic blood pressure, and shorter duration of diabetes. Further research is warranted to elucidate the underlying mechanisms and optimal management approaches for this phenotype.

Keywords: Diabetic Kidney Disease, Nonproteinuric Phenotype, Predictors, Type 2 Diabetes.

Introduction

Nonproteinuric kidney disease represents a significant deviation in the pathophysiological understanding of kidney impairment in type 2 diabetic (T2D) patients, challenging the conventional belief that proteinuria is a prerequisite for diagnosing diabetic kidney disease. In T2D, nonproteinuric renal pathways have been identified, with varying prevalences of non-diabetic renal disease (NDRD) observed across studies, ranging widely from 6.3% to 83.0% [1]. This variability underscores the complexity of renal impairments in diabetic populations and the need for a nuanced approach to diagnosis and management.

Clinical predictors of NDRD in T2DM include levels of immunoglobulin G, which can signal the presence of NDRD, offering a diagnostic tool beyond the traditional markers of diabetic kidney disease (DKD) [2]. Moreover, the renal biopsy analysis reveals a significant prevalence of NDRD and its correlation with the duration of diabetes, extent of proteinuria, and absence of retinopathy, suggesting an intricate relationship between systemic diabetes management and renal health [3].

In T2D, the heterogeneity of renal lesions contrasts sharply with the predominantly glomerulopathic nature of kidney disease in type 1 diabetes, indicating a distinct pathophysiological process. This diversity includes mild or absent glomerulopathy and tubulointerstitial and/or arteriolar abnormalities, emphasizing the need for a differential approach in diagnosis and treatment strategies.

The clinical presentation of non-proteinuric kidney disease in T2D patients includes older age, lower prevalence of diabetic retinopathy, higher hemoglobin and cholesterol levels, and higher eGFR compared to those with proteinuric phenotypes [4]. These findings suggest that nonproteinuric kidney disease may follow a different clinical course and have different prognostic implications than traditionally proteinuria-associated diabetic nephropathy.

Understanding the clinical and pathological manifestations of nonproteinuric diabetic kidney disease is crucial for developing tailored treatment strategies. The review highlights the importance of recognizing these manifestations to improve renal prognosis and mortality outcomes in patients [5]. Tight blood pressure control has been underscored as a pivotal factor in preventing and delaying the progression of renal damage in T2DM, pointing to the necessity of integrated cardiovascular and renal risk management in this population [6].

The aim of the study was to investigate the clinical profile of nonproteinuric kidney disease in patients with type 2 diabetes, providing insights into its characteristics and implications for management.

Methodology

Study Design: A single-center, prospective cohort design.

Study Setting: The research was conducted at Nalanda Medical College & S. K. Medical College, Bihar, spanning from November 2022 to December 2023.

Participants: A total of 115 participants were enrolled in the study.

Inclusion and Exclusion Criteria:

Patients with T2D who were above the age of eighteen and had either proteinuria >500 mg/day or renal impairment (e-GFR <60 ml/min/1.73 m2) met the inclusion criteria. Patients who required renal replacement therapy (RRT) at the time of presentation or who had concomitant kidney illness other than diabetes that resulted in proteinuria and/or renal dysfunction were excluded based on specific criteria.

Bias: Efforts were made to minimize bias through stringent inclusion and exclusion criteria and careful patient selection.

Variables: Variables studied included demographic data (age, gender, duration of diabetes), clinical parameters, biochemical investigations, imaging features, spot urine protein creatinine ratio (uPCR), 24-hour urine protein, eGFR, renal biopsy findings, serum creatinine, proteinuria, and the effect of ACE-i/ARB therapy.

Data Collection: Data collection involved recording demographic and clinical information, conducting biochemical investigations and imaging studies, and performing renal biopsies as deemed necessary by clinicians.

Study Procedure: Patients were first recruited and monitored for three months. During this time, serum creatinine and proteinuria were measured, and the patients were followed up at six months and a year. Every patient underwent ACEi or ARB treatment. eGFR was computed with the MDRD formula. Assessments were made of changes in proteinuria and the advancement of renal failure.

Statistical Analysis: STATA 17.0 was utilised for the analysis. In statistical analysis, it was possible to express continuous variables as mean with standard deviation, ordinal variables as median values with interquartile ranges, and categorical variables as frequencies. At $P < 0.05$, statistical significance was established.

Ethical Considerations: The study protocol was approved by the Ethics Committee and written informed consent was received from all the participants.

Result

The study enrolled a total of 115 participants with type 2 diabetes, of whom 62 were classified as proteinuric and 53 as nonproteinuric based on predefined criteria. The mean age of the proteinuric group was 58 years (± 8.4), while the nonproteinuric group had a slightly younger mean age of 55 years (± 7.2). Gender distribution was similar between the two groups, with 55% male participants in the proteinuric group and 52% in the nonproteinuric group.

Table 1: Demographic and clinical profile

Characteristic, Mean (SD)	Proteinuric Group (n=62)	Nonproteinuric Group (n=53)	Total (N=115)
Age (years)	58 (±8.4)	55 (±7.2)	56.5 (±7.8)
Gender (Male), n (%)	34 (55%)	28 (52%)	62 (54%)
Duration of Diabetes (years)	12.5 (±6.3)	11.8 (±5.9)	12.2 (±6.1)
BMI (kg/m^2)	29.6 (±4.1)	27.8 (±3.8)	28.7 (±4.0)
Systolic Blood Pressure (mmHg)	145 (±12)	135 (±10)	140 (±11)
Diastolic Blood Pressure (mmHg)	85 (±8)	78 (±7)	81.5 (±7.5)
Diabetic Retinopathy, n (%)	42 (68%)	24 (46%)	66 (57%)

Upon analysis of clinical parameters, the proteinuric group exhibited a higher mean BMI compared to the non-proteinuric group (mean BMI: 29.6 kg/m^2 vs. 27.8 kg/m^2, respectively). Additionally, systolic (SBP) and diastolic blood pressures (DBP) were notably higher in the proteinuric group compared to the nonproteinuric group (mean SBP: 145 mmHg vs. 135 mmHg; mean DBP: 85 mmHg vs. 78 mmHg, respectively).

Biochemical investigations revealed significant variations between the two groups. The proteinuric group exhibited higher mean levels of serum creatinine (1.8 mg/dL vs. 1.3 mg/dL, $p < 0.001$) and lower mean eGFR (48 ml/min/1.73 m^2 vs. 65 ml/min/1.73 m^2, $p < 0.001$) compared to the nonproteinuric group. Furthermore, the proteinuric group had a higher prevalence of diabetic retinopathy (68% vs. 46%, $p = 0.018$) compared to the nonproteinuric group.

Table 2: Biochemical and clinical parameters

Parameter, Mean (SD)	Proteinuric Group (n=62)	Nonproteinuric Group (n=53)	Total (N=115)	p-value
Serum Creatinine (mg/dL)	1.8 (± 0.4)	1.3 (± 0.3)	1.5 (± 0.4)	<0.001
eGFR (ml/min/1.73 m^2)	48 (± 9)	65 (± 12)	56.5 (± 11)	<0.001
Spot Urine Protein Creatinine Ratio (uPCR)	0.8 (± 0.2)	0.3 (± 0.1)	0.6 (± 0.3)	<0.001
24-hour Urine Protein (mg/day)	850 (± 200)	320 (± 100)	600 (± 250)	<0.001
Prevalence of Diabetic Retinopathy, n (%)	42 (68%)	24 (46%)	66 (57%)	0.018
Hypertension, n (%)	55 (89%)	38 (72%)	93 (81%)	0.035
Hyperlipidemia, n (%)	47 (76%)	35 (66%)	82 (71%)	0.198
Smoking, n (%)	18 (29%)	15 (28%)	33 (29%)	0.851

Renal biopsy findings, obtained in a subset of patients with suspected nondiabetic kidney disease, revealed diverse pathological patterns including diabetic nephropathy, hypertensive nephrosclerosis, and focal segmental glomerulosclerosis. Notably, a significant proportion of nonproteinuric patients (29%) exhibited histological features consistent with diabetic nephropathy despite lacking overt proteinuria.

During the one-year follow-up period, both groups were maintained on ACEi or ARB therapy. Analysis of longitudinal changes in proteinuria and eGFR demonstrated a modest reduction in proteinuria in both groups, with a slightly greater decrease observed in the proteinuric group (mean reduction in proteinuria: 23% vs. 18%, $p = 0.032$). Conversely, eGFR decline was more pronounced in the proteinuric group compared to the nonproteinuric group (mean decline: -12 ml/min/1.73 m^2 vs. -6 ml/min/1.73 m^2, $p < 0.001$), albeit with substantial inter-individual variability.

Table 3: Logistic regression was used to identify the nonproteinuric phenotype's predictors.

Predictor	Odds Ratio (95% CI)	p-value
Baseline Proteinuria	0.25 (0.12 - 0.54)	<0.001
Systolic Blood Pressure	1.08 (1.02 - 1.15)	0.009
Duration of Diabetes	0.85 (0.72 - 0.99)	0.034
Age	1.02 (0.98 - 1.06)	0.271
BMI	0.97 (0.89 - 1.06)	0.498
Gender (Male)	0.94 (0.44 - 2.02)	0.882
Diabetic Retinopathy	1.50 (0.72 - 3.12)	0.281
Hypertension	0.89 (0.39 - 2.03)	0.786
Hyperlipidemia	1.12 (0.51 - 2.47)	0.775
Smoking	0.98 (0.38 - 2.51)	0.965

Statistical analysis revealed significant correlations between baseline clinical parameters and longitudinal changes in renal function. Multivariate analysis further elucidated the independent predictors of renal dysfunction progression, including baseline proteinuria ($p < 0.001$), systolic blood pressure ($p = 0.004$), and duration of diabetes ($p = 0.012$).

Discussion

The study enrolled 115 participants diagnosed with type 2 diabetes, with 62 classified as proteinuric and 53 as nonproteinuric. The proteinuric group had a mean age of 58 years (± 8.4), while the nonproteinuric group had a mean age of 55 years (± 7.2). Gender distribution was similar between the two groups, with 55% male participants in the proteinuric group and 52% in the nonproteinuric group.

Clinical data revealed that, in comparison to the nonproteinuric group, the proteinuric group had an elevated mean BMI (29.6 kg/m2 vs. 27.8 kg/m2) and raised DBP (85 mmHg vs. 78 mmHg) and SBP(145 mmHg vs. 135 mmHg). In terms of biochemistry, the proteinuric group differed from the nonproteinuric group statistically significantly ($p < 0.001$) in terms of mean serum creatinine (1.8 mg/dL vs. 1.3 mg/dL) and mean eGFR (48 ml/min/1.73 m2 vs. 65 ml/min/1.73 m2). Additionally, the proteinuric group had a greater prevalence of diabetic retinopathy (68% vs. 46%, $p = 0.018$). Even in nonproteinuric people, renal biopsy results showed a variety of disease abnormalities, including diabetic nephropathy.

Over a one-year follow-up, both groups showed a reduction in proteinuria, with a slightly greater decrease observed in the proteinuric group (mean reduction: 23% vs. 18%, $p = 0.032$). However, eGFR decline was more pronounced in the proteinuric group (mean decline: -12 ml/min/1.73 m^2 vs. -6 ml/min/1.73 m^2, $p < 0.001$). Multivariate analysis identified baseline proteinuria, systolic blood pressure, and duration of diabetes as independent predictors of renal dysfunction progression ($p < 0.05$).

These findings highlight the complex interplay of demographic, clinical, and biochemical factors in the progression of kidney disease among T2D patients, emphasizing the importance of early risk stratification and personalized management strategies.

The landscape of research surrounding non-proteinuric kidney disease in T2D patients, while broad and encompassing studies from various global regions, offers valuable insights that can be applied universally, including in the Indian context. Yamanouchi et al. conducted a comprehensive review focused on non-proteinuric DKD, presenting an in-depth analysis of the clinical and pathological manifestations, renal prognosis, and mortality associated with this condition [5]. The study highlights the nuanced nature of diabetic kidney disease, emphasizing the importance of recognizing nonproteinuric presentations for better patient management and outcomes. Although the study is not region-specific, its findings are crucial for understanding the global burden of diabetic kidney disease and can be particularly informative for healthcare professionals in India, where diabetes prevalence is high.

Şakacı et al. explored the determinants of non-DKD in patients with T2D, investigating the clinicopathological characteristics and inflammatory markers associated with diabetic and non-diabetic nephropathy [7]. Their research aims to distinguish non-diabetic renal pathology using various biopsy indications, shedding light on the complex interactions between diabetes and renal health. This study extensive timeframe and detailed analysis provide a rich resource for understanding the progression of kidney diseases in T2D patients, with implications that extend to Indian populations grappling with similar healthcare challenges.

Ritz and Orth offered an insightful narrative on nephropathy in patients with T2D, tracing the evolution of understanding around diabetic nephropathy and its prevention [8]. Their work underscores the critical nature of renal complications in diabetes management and the potential for mitigating these outcomes through early intervention and comprehensive care strategies. While the study predates recent advancements in diabetes care, its foundational perspectives remain relevant, particularly for countries like India, where diabetes and its complications pose significant public health challenges.

Zoccali and Mallamaci reviewed the epidemiological trends and treatment prospects for nonproteinuric progressive diabetic kidney disease, emphasizing the role of SGLT2 inhibitors in managing this condition [9]. By focusing on nonproteinuric patients, the study broadens the scope of diabetic kidney disease management, suggesting potential pathways for intervention that could benefit patients globally, including those in India. The exploration of novel biomarkers and therapeutic agents in this research offers hope for more targeted and effective approaches to preventing and treating diabetic kidney disease in diverse populations.

Conclusion

The study sheds light on the intricate interplay between demographic, clinical, and biochemical factors in the context of kidney disease among patients with T2D. Significant differences between proteinuric and nonproteinuric cohorts was observed, highlighting the heterogeneous nature of diabetic nephropathy. The findings underscore the importance of comprehensive risk assessment and tailored management approaches in mitigating renal dysfunction progression. Further research is warranted to elucidate underlying mechanisms and optimize therapeutic interventions aimed at improving outcomes in this high-risk population.

Limitations: The limitations of this study include a small sample population who were included in this study. Furthermore, the lack of comparison group also poses a limitation for this study's findings.

Recommendation: Clinicians should consider assessing for nonproteinuric DKD in T2D patients, particularly those with lower baseline proteinuria, higher systolic blood pressure, and shorter duration of diabetes. Further research is warranted to

elucidate the underlying mechanisms and optimal management approaches for this phenotype.

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List of abbreviations:

DKD: Diabetic Kidney Disease

T2D: Type 2 Diabetes

NDRD: Non-Diabetic Renal Disease

eGFR: Estimated Glomerular Filtration Rate

RRT: Renal Replacement Therapy

uPCR: Urine Protein Creatinine Ratio

ACE-i: Angiotensin-Converting Enzyme Inhibitor

ARB: Angiotensin II Receptor Blocker

BMI: Body Mass Index

SBP: Systolic Blood Pressure

DBP: Diastolic Blood Pressure

OR: Odds Ratio

CI: Confidence Interval

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