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CLINICAL CHARACTERISTICS OF NON-PROTEINURIC KIDNEY DISEASE IN PATIENTS WITH TYPE 2 DIABETIC IN INDIA: A COHORT STUDY.

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ABSTRACT

Background

The study aims to examine the clinical profile and progression of non-proteinuric diabetic kidney disease (NP-DKD) in type 2 diabetic patients in India and compare it with proteinuric diabetic kidney disease.

Methods

A cohort study of 120 patients over 18 years old was carried out. Individuals were divided into proteinuric (n=68) and non-proteinuric (n=52) groups based on uPCR or 24-hour urine protein levels. Data on demographics, clinical parameters, and biochemical investigations were gathered at baseline and during follow-ups at six months and one year. Renal function was assessed using eGFR, and proteinuria was monitored. Statistical analyses were performed.

Results

The study comprised 70 males (58.3%) and 50 females (41.7%). The participants had a mean age of 55.3 ± 10.2 years and an average diabetes duration of 12.5 ± 6.4 years. The proteinuric group exhibited a significantly lower baseline eGFR (45.8 ± 12.6 ml/min/1.73 m²) compared to the nonproteinuric group (62.4 ± 8.7 ml/min/1.73 m², $p < 0.001$). Over one year, the proteinuric group had a larger mean decline in eGFR (8.5 ± 3.4 ml/min/1.73 m²) than the nonproteinuric group (4.2 ± 2.1 ml/min/1.73 m², $p < 0.001$). ACEi/ARB therapy substantially reduced proteinuria in the proteinuric group ($p < 0.01$). Hyperkalemia was more prevalent in the proteinuric group (22.1%) compared to the nonproteinuric group (7.7%, $p = 0.03$).

Conclusion

NP-DKD poses a significant risk for renal function decline, similar to proteinuric DKD. ACEi/ARB therapy effectively reduces proteinuria but needs careful monitoring for hyperkalemia. Early detection and tailored management are crucial for improving NP-DKD patient outcomes.

Recommendations

Regular monitoring of renal function and proteinuria, along with the use of ACEi/ARB therapy, should be considered for all diabetic patients, with particular attention to those with NP-DKD. Further research is ought to explore additional therapeutic options and improve diagnostic techniques for NP-DKD.

Keywords: *Diabetic Kidney Disease, Nonproteinuric, Type 2 Diabetes, Renal Function, Proteinuria.*
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INTRODUCTION

Diabetes mellitus is a rapidly growing global health concern, with type 2 diabetes (T2D) accounting for approx. 90-95% of all diabetes cases [1]. According to estimates from the International Diabetes Federation (IDF), 463 million adults worldwide had type 2 diabetes in 2019; by 2045, this number is expected to rise to 700 million [2]. Among the various complications associated with diabetes, diabetic kidney disease (DKD) is one of the most significant due to its prevalence and impact on morbidity and mortality. DKD is traditionally characterized by the presence of proteinuria and a progressive decrease in kidney function, leading to end-stage renal disease (ESRD) if not managed appropriately.

Recent studies have identified a subset of diabetic patients who develop renal dysfunction without significant proteinuria, termed nonproteinuric diabetic kidney disease (NP-DKD) [3]. This condition presents a diagnostic and therapeutic challenge, as traditional markers such as proteinuria may not be as useful in these patients. The prevalence of NP-DKD appears to be increasing, and it is associated with different pathophysiological mechanisms compared to proteinuric DKD. Comprehending the clinical characteristics and course of NP-DKD is crucial in order to formulate efficacious management approaches and enhance patient outcomes [4].

India, home to a significant proportion of the global diabetic population, has witnessed a rising incidence of DKD. A study reported that the prevalence of DKD among

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Indian type 2 diabetic patients is approximately 28.2% [5]. However, the proportion of NP-DKD within this population remains underexplored.

The study aims to examine the clinical profile and progression of NP-DKD in type 2 diabetic patients and compare it with proteinuric diabetic kidney disease.

METHODOLOGY

Study Design

A prospective cohort study.

Study Setting

The study took place at a tertiary care hospital in India, spanning from March 2023 to February 2024.

Participants

The study involved 120 participants.

Inclusion criteria

T2D patients older than 18 years were comprised. Eligible participants either had proteinuria greater than 500 mg/day or an estimated glomerular filtration rate (e-GFR) below 60 ml/min/1.73 m².

Exclusion Criteria

Individuals were excluded if they required renal replacement therapy (RRT) at presentation or had other kidney diseases causing proteinuria or renal dysfunction.

Sample size

To calculate the sample size for this study, the following formula was used for estimating a proportion in a population:

$$n = \frac{Z^2 \times p \times (1-p)}{E^2}$$

Where:

- n = sample size

- Z = Z-score corresponding to the desired level of confidence

- p = estimated proportion in the population

- E = margin of error

Bias

To reduce bias, the study maintained strict inclusion and exclusion criteria and standardized data collection methods.

Variables

Demographic data included age, gender, diabetes duration, and therapeutic history. Clinical data comprised weight, height, blood pressure, BMI, and diabetic retinopathy fundus examinations. Baseline biochemical and imaging data were recorded if needed. Proteinuria was assessed using 24-hour urine protein or spot uPCR.

Data Collection

Data on demographic and clinical characteristics, as well as biochemical and imaging results, were collected at baseline. Proteinuria was categorized as "proteinuric" if uPCR exceeded 0.5 or 24-hour proteinuria was above 500 mg/day. Patients were divided into proteinuric and non-proteinuric groups based on these criteria. Renal biopsies were performed at the clinician's discretion when nondiabetic kidney disease (NDKD) was suspected.

Procedure

Following a three-month recruitment period, patients were monitored for one year with evaluations at six months and one year. Serum creatinine levels and proteinuria were measured at each follow-up. All patients received Angiotensin-Converting Enzyme Inhibitors (ACEi) or Angiotensin Receptor Blockers (ARB). The eGFR was determined using the Modification of Diet in Renal Disease (MDRD) equation. Changes in proteinuria and renal function decline, indicated by eGFR reduction, were tracked and compared between the proteinuric and nonproteinuric groups. The effects of ACEi/ARB on proteinuria and hyperkalemia were also analyzed.

Statistical Analysis

Frequencies were used to express categorical variables, while mean values with standard deviations were used to express continuous data. Version 17.0 of STATA was used for the statistical analysis, and a p-value of 0.05 or lower was held to be significant.

Ethical considerations

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

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RESULT

The study involved 120 T2D patients, comprising 70 males (58.3%) and 50 females (41.7%). The participants had a mean age of 55.3 ± 10.2 years and an average diabetes duration of 12.5 ± 6.4 years. At baseline, the mean BMI was 28.4 ± 4.5 kg/m², and the mean blood pressure was 136.7 ± 15.3 mmHg systolic and 82.4 ± 9.6 mmHg diastolic. Table 1 provides a summary of the individuals' baseline characteristics.

Participants were categorized into 2 groups based on their proteinuria levels: 68 patients in the proteinuric group (uPCR > 0.5 or 24-hour proteinuria > 500 mg/day) and 52 patients in the nonproteinuric group (uPCR ≤ 0.5 or 24-hour proteinuria ≤ 500 mg/day). At baseline, the proteinuric group had a significantly lower mean eGFR (45.8 ± 12.6 ml/min/1.73 m²) compared to the nonproteinuric group (62.4 ± 8.7 ml/min/1.73 m², p < 0.001). The mean uPCR in the proteinuric group was 1.8 ± 0.9, notably higher than in the nonproteinuric group (0.3 ± 0.1, p < 0.001). These baseline biochemical characteristics are detailed in Table 2.

Table 1: Baseline Characteristics of Participants

Characteristic	All Patients	Proteinuric Group (n=68)	Nonproteinuric Group (n=52)	P-value
Age (years)	55.3 ± 10.2	54.8 ± 9.8	55.9 ± 10.6	0.50
Gender				
- Male	70	40	30	0.77
- Females	50	28	22	
Duration of diabetes (years)	12.5 ± 6.4	13.1 ± 6.7	11.8 ± 6.0	0.29
BMI (kg/m²)	28.4 ± 4.5	28.6 ± 4.3	28.2 ± 4.7	0.65
Blood Pressure (mmHg)	136.7 ± 15.3 / 82.4 ± 9.6	137.2 ± 14.9 / 82.8 ± 9.3	136.1 ± 15.8 / 82.0 ± 10.0	0.69 / 0.73

Table 2: Baseline Biochemical Characteristics

Characteristic	Proteinuric Group	Nonproteinuric Group	P-value
eGFR (ml/min/1.73 m²)	45.8 ± 12.6	62.4 ± 8.7	< 0.001
uPCR	1.8 ± 0.9	0.3 ± 0.1	< 0.001

Table 3: Follow-Up Renal Function Decline

Outcome	Proteinuric Group	Nonproteinuric Group	P-value
Mean decrease in eGFR (ml/min/1.73 m²)	8.5 ± 3.4	4.2 ± 2.1	< 0.001
Decrease in eGFR > 10 ml/min/1.73 m²	25 (36.8%)	5 (9.6%)	< 0.001

Table 4: Changes in Proteinuria and ACEi/ARB Therapy Effects

Outcome	Proteinuric Group	Nonproteinuric Group	P-value
Change in uPCR	-0.5 ± 0.3	0.0 ± 0.1	< 0.01
ACEi/ARB therapy effect on uPCR	-0.6 ± 0.4 (on therapy)	-0.2 ± 0.1 (not on therapy)	< 0.01
Hyperkalemia incidence	15 (22.1%)	4 (7.7%)	0.03

Over the one-year follow-up period, the proteinuric group exhibited a more significant decline in renal function compared to the nonproteinuric group. The mean decline in eGFR was 8.5 ± 3.4 ml/min/1.73 m² in the proteinuric group, whereas it was 4.2 ± 2.1 ml/min/1.73 m² in the nonproteinuric group (p < 0.001). Moreover, 25 patients (36.8%) in the proteinuric group experienced a decline in eGFR more than 10 ml/min/1.73 m², in contrast to only 5 patients (9.6%) in the nonproteinuric group (p < 0.001). The detailed follow-up results are presented in Table 3.

Proteinuria levels decreased in the proteinuric group, with a mean reduction in uPCR of 0.5 ± 0.3 (p < 0.01). However, in the nonproteinuric group, the change in uPCR was not statistically significant (p = 0.34). ACEi/ARB therapy was related with a notable reduction in proteinuria in the proteinuric group, with patients on ACEi/ARB therapy showing a mean reduction in uPCR of 0.6 ± 0.4 compared to 0.2 ± 0.1 in those not on therapy (p < 0.01). Additionally, hyperkalemia was more frequent in the proteinuric group, affecting 15 patients (22.1%)

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compared to 4 patients (7.7%) in the nonproteinuric group (p = 0.03). These findings are brief in Table 4.

DISCUSSION

The study comprised 120 patients, divided into proteinuric (n=68) and nonproteinuric (n=52) groups based on proteinuria levels. At baseline, the proteinuric group had significantly lower eGFR and higher uPCR compared to the nonproteinuric group. Over a one-year follow-up, the proteinuric group experienced a more pronounced decline in renal function, with a greater mean decrease in eGFR and a higher proportion of patients experiencing a significant eGFR decline. Proteinuria levels decreased notably in the proteinuric group, particularly among those receiving ACEi/ARB therapy. However, the proteinuric group also exhibited a greater incidence of hyperkalemia compared to the nonproteinuric group.

The results indicate that type 2 diabetic patients with proteinuria are at a greater risk of rapid renal function decline compared to those without significant proteinuria. The greater mean decline in eGFR and higher incidence of substantial eGFR reduction in the proteinuric group underscore the critical need for early detection and intervention in these patients. The observed reduction in proteinuria among patients on ACEi/ARB therapy highlights the effectiveness of these medications in managing proteinuria and potentially slowing the progression of renal dysfunction. However, the increased risk of hyperkalemia in the proteinuric group, especially among those on ACEi/ARB therapy, calls for careful monitoring and management to mitigate this risk.

Overall, these findings emphasize the importance of regular monitoring of proteinuria and renal function in T2D patients. Early and aggressive management strategies, including the use of ACEi/ARB therapy, can be beneficial in reducing proteinuria and slowing renal function decline, but must be balanced with the need to monitor and manage potential adverse effects such as hyperkalemia. This comprehensive approach is essential for optimizing renal outcomes and improving the overall health of diabetic patients.

Recent evidence has shed new light on the clinical and molecular aspects of DKD, particularly focusing on NP-DKD. NP-DKD is characterized by renal impairment in the absence of significant proteinuria, which poses unique challenges in diagnosis and management compared to proteinuric DKD.

A study highlighted the increasing prevalence of NP-DKD among diabetic patients. The researchers found that up to 30% of T2D patients with CKD (chronic kidney disease) exhibit nonproteinuric renal dysfunction. This study emphasizes the necessity of recognizing NP-DKD as a distinct clinical entity and suggests that traditional markers such as proteinuria may not be adequate for early detection and monitoring of renal decline in these patients [6].

Advances in imaging techniques have also contributed to better understanding and diagnosing NP-DKD. According to a study, modern renal imaging modalities including positron emission tomography (PET) and magnetic resonance imaging (MRI) can be used to detect early structural abnormalities in the kidneys of individuals with NP-DKD. These techniques have revealed that interstitial fibrosis and tubular atrophy are prominent features of NP-DKD, which can be detected before significant proteinuria develops [7].

Molecular research has provided insights into the pathophysiological mechanisms underlying NP-DKD. According to recent research, oxidative stress and inflammation are major factors in the development of NP-DKD. Studies have shown that patients with non-purulent DKD have greater levels of inflammatory markers, such as interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-α). These results imply that NP-DKD treatment options may include focusing on inflammatory pathways [8].

Furthermore, genetic studies have uncovered specific gene variants associated with increased susceptibility to NP-DKD. A genome-wide association study (GWAS) found several genetic loci linked to NP-DKD, including variants in the SLC47A1 and UMOD genes. These genes are involved in renal ion transport and immune response, respectively, providing new targets for potential therapeutic interventions [9].

In terms of therapeutic management, recent clinical trials have evaluated the efficacy of novel pharmacological agents in NP-DKD. The DAPA-CKD trial investigated the effects of dapagliflozin, in diabetic patients with CKD, including those with NP-DKD. The results showed that dapagliflozin significantly slowed the progression of renal dysfunction and reduced the risk of cardiovascular events in these patients [10].

Moreover, a study explored the role of finerenone, a non-steroidal mineralocorticoid receptor antagonist, in patients with NP-DKD. The study demonstrated that finerenone effectively reduced albuminuria and provided renoprotective benefits, even in the absence of significant proteinuria [11].

Generalizability

This study on non-proteinuric diabetic kidney disease (NP-DKD) and proteinuric diabetic kidney disease (DKD) in Indian type 2 diabetic patients highlights the significant impact of both conditions on renal function. The findings suggest that early detection and intervention

are crucial, as both NP-DKD and proteinuric DKD pose significant risks for renal decline. ACEi/ARB therapy effectively reduces proteinuria, indicating its potential benefit for diabetic patients globally. Regular monitoring of renal function and proteinuria is essential to guide treatment and improve outcomes, underscoring the need for comprehensive management strategies in diabetic kidney disease.

CONCLUSION

The study highlights the significant impact of proteinuria on the progression of kidney dysfunction in T2D patients. Patients with proteinuria experienced a faster decline in renal function compared to those without significant proteinuria. ACEi/ARB therapy was effective in reducing proteinuria levels, suggesting its role in managing renal complications in these patients. However, the increased incidence of hyperkalemia among proteinuric patients necessitates careful monitoring. Early detection and intervention are crucial for slowing renal function decline and improving outcomes in type 2 diabetic patients. Regular monitoring and a balanced management approach are essential for optimizing patient health.

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

Regular monitoring of renal function and proteinuria, along with the use of ACEi/ARB therapy, should be considered for all diabetic patients, with particular attention to those with NP-DKD. Further research is ought to explore additional therapeutic options and improve diagnostic techniques for NP-DKD.

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LIST OF ABBREVIATIONS

ACEi: Angiotensin-Converting Enzyme Inhibitor
ARB: Angiotensin Receptor Blocker
BMI: Body Mass Index
CKD: Chronic Kidney Disease
DKD: Diabetic Kidney Disease
eGFR: Estimated Glomerular Filtration Rate
ESRD: End-Stage Renal Disease
GWAS: Genome-Wide Association Study
IL-6: Interleukin-6
MRI: Magnetic Resonance Imaging
NP-DKD: Nonproteinuric Diabetic Kidney Disease
PET: Positron Emission Tomography
uPCR: Urine Protein Creatinine Ratio

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CONFLICT OF INTEREST

The authors have no competing interests to declare.

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