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Original Research Article

A Hospital Based Clinico-Demographic Assessment of Non Proteinuric Kidney Disease in Type 2 Diabetic Patients

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Abstract

Aim: This study aimed to evaluate the demographic and clinical characteristics of non proteinuric kidney disease in type 2 diabetic patients in Bihar region.

Material & methods: This study was a single-center, prospective cohort study conducted in the Department of Nephrology for the period of 2 years. Written and informed consent were taken from all participants. In this single-center, prospective observational study, 500 consecutive type 2 diabetic patients with either overt proteinuria (>500 mg/day) and/or renal dysfunction (eGFR <60 ml/min/1.73 m2) were recruited.

Results: Both the groups were similar in terms of gender, duration of diabetes, comorbidities, body mass index (BMI), blood pressure control, and glycemic control. The nonproteinuric group was older, had lesser prevalence of diabetic retinopathy ($P < 0.001$), higher hemoglobin levels and higher cholesterol levels. We studied the predictors of progression of renal dysfunction, but no variable was found to be significantly associated with renal dysfunction. We applied logistic regression analysis to find predictors of nonproteinuric kidney disease and found that the absence of retinopathy and presence of higher hemoglobin predicted non proteinuric phenotype.

Conclusion: Most patients with diabetic kidney disease (DKD) have proteinuria, but approximately 20% have chronic kidney disease (CKD) without proteinuria. Simultaneous assessment of both albuminuria and eGFR is required in all diabetic patients. Studies are required to understand the utility of newer markers either alone or in combination with proteinuria to define nonproteinuric DKD.

Keywords: Diabetic nephropathy, nonproteinuric kidney disease, type 2 diabetes mellitus.

Introduction

Diabetes mellitus (DM) is the commonest cause of chronic kidney disease (CKD) and end-stage renal disease (ESRD) worldwide. Approximately 40% of all patients diagnosed with type 2 diabetes mellitus (T2DM) eventually develop diabetic kidney disease (DKD); this condition may lead to end-stage renal failure (ESRF), cardiovascular disease and premature death. [1] Early detection of diabetic kidney disease (DKD) is of paramount importance to slow the rate of progression. Albuminuria is widely regarded as the earliest marker of DKD and is used as a screening test. [2] Albuminuria followed by a decline in glomerular filtration rate (GFR), has been long considered to be the pathognomonic sign of DKD. [3-7] Proteinuria, or macroalbuminuria, has been considered to be the clinical hallmark of diabetic kidney disease and an independent risk factor for ESKD. [8,9] Patients with diabetic kidney disease are believed to develop proteinuria prior to renal function loss. [10]

This phenotype of diabetic kidney disease suggests that there is an association between renal function loss and level of albuminuria in patients with diabetes and highlight the need for broader understanding of renal function loss apart from those related to an increase in albuminuria. The decline in GFR can occur in the absence of proteinuria. The development of advanced CKD classically follows overt proteinuria. [11] The renal dysfunction in NP-DKD is explained by the presence of adequate tubular function which reabsorbs albumin and/or the occurrence of macroangiopathic lesions in the kidneys. [12] DN was initially considered to begin with proteinuria preceding the progression of renal insufficiency [estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m2]. The natural history was divided

into normoalbuminuria (urinary albumin-to-creatinine ratio [UACR] <30 mg/g), microalbuminuria (UACR 30–300 mg/g), and macroalbuminuria (UACR >300 mg/g), which was mainly based on the typical progression course of type 1 DM. [13]

However, this concept of the clinical paradigm has changed over the last decades, and it has been noted that DM patients without proteinuria could also have progressive renal insufficiency. Therefore, the latest diagnostic criteria for diabetic kidney disease (DKD) include low eGFR or the persistent presence of elevated urinary albumin excretion (albuminuria). [14] Nonproteinuric DKD was defined as an eGFR <60 mL/min/1.73 m2 with a UACR <300 mg/g. [15] As a diagnosis term, DKD covered both clinical diagnosis and histological diagnosis (DN).

In spite of this high prevalence, data regarding the clinical characteristics of these patients are lacking. This leads to insufficient knowledge about treating this subgroup of patients as they are often excluded from the classic DKD trials. The very existence, prevalence, and clinical profile of this non proteinuric kidney disease phenotype are not well defined, more so in the population of Bihar region.

Hence the aim of study was to evaluate the demographic and clinical characteristics of non proteinuric kidney disease in type 2 diabetic patient of Bihar region.

Material & Methods

This study was a single-center, prospective cohort study conducted in the Department of Nephrology at Patna Medical College and Hospital,Patna, Bihar, India for a period of 2 years. Written and informed consent was sought from all participants. In this single-center, prospective observational study, 500 consecutive type 2 diabetic patients with either overt proteinuria (>500 mg/day) and/or renal dysfunction eGFR <60 ml/min/1.73 m2) were recruited. Patients requiring renal replacement therapy (RRT) at presentation or having associated kidney disease other than diabetes causing proteinuria and/or renal dysfunction were excluded.

Demographic data including age, gender, duration of diabetes, and treatment history and clinical data including weight, height, body mass index (BMI), blood pressure, and fundus examination for diabetic retinopathy were collected. Biochemical investigations at baseline and imaging features (if required) on ultrasound were documented. Spot urine protein creatinine ratio (uPCR) or 24-h urine protein was used to assess the degree of proteinuria and labeled “proteinuric” if uPCR was >0.5 or 24-h proteinuria was >500 mg/day. According to this definition, patients with eGFR <60 ml/min/1.73 m2 (not all had eGFR <60 ml) or proteinuria greater than 500 mg/day were divided into two groups: proteinuric and non proteinuric. Renal biopsy was done as per clinician’s advice only if there was suspicion of nondiabetic kidney disease (NDKD). After an initial recruitment period of 3 months, patients were followed up for the next 1 year (at 6 months and 1 year) and their serum creatinine and proteinuria were recorded. All patients were on Angiotensin converting enzyme inhibitors (ACEi) or Angiotensin receptor blocker (ARB) therapy. eGFR was calculated using the Modification of Diet in Renal Disease (MDRD) equation. Change in proteinuria and progression of renal dysfunction in terms of decline in eGFR were studied and compared between the two groups. The effect of ACE-i/ARB on proteinuria and hyperkalemia was also studied. Approval for the study was taken from the Institute Ethics Committee.

Statistical Analysis

Categorical variables were expressed as frequencies, continuous variables as mean values with standard deviation, and ordinal variables as median values with interquartile ranges. Groups with normally distributed variables were compared using t-test. Wilcoxon test was used for non-normally distributed variables, and the Chi-squared test for categorical variables. Spearman correlation was used for univariate analysis. Multivariate analysis was performed with logistic regression analysis. Statistical analysis was performed with the STATA, version. 17.0. For all comparisons, P < 0.05 was considered statistically significant.

Results

Table 1: Baseline demographic and clinical parameters of the study population

Parameter	All patients (n=500)	Nonproteinuric (n=100)	Proteinuric (n=400)	P
Age (in years) (mean± SD)	54.16±12.48	55.45±12.08	53.57±11.66	0.0132
Males, n (%)	400 (80%)	80 (80%)	320 (80%)	0.832
Duration of diabetes mellitus (years), median (range)	11 (5-15)	8.86±7.08	10.18±5.65	0.5335
Hypertension, n (%)	375 (75%)	65 (65%)	310 (77.50%)	0.120
CAD, n (%)	75 (15.5%)	22 (22%)	53 (13.25%)	0.122
CVA, n (%)	5 (1%)	1 (1%)	4 (1%)	0.165
BMI (kg/m2) (mean±SD)	25.35±4.32	25.75±4.64	25.24±4.24	0.175
Blood pressure control (<140/90	100 (20.85%)	15 (15%)	85 (21.25%)	0.068

mmHg), n (%)				
Diabetic retinopathy, n (%)	350 (67.25%)	48 (48%)	302 (75.50%)	<0.001
Hemoglobin (g/dl) (mean±SD)	10.4±3	11.33±1.91	10.49±2.05	<0.001
Serum albumin (g/dl) (mean±SD)	3.84±0.76	3.98±0.82	3.78±0.72	0.0626
eGFR (ml/min/1.73 m2) (mean±SD)	40.22±22.78	42.88±19.41	40.6±23.77	0.3324
Serum potassium (mEq/dl) (mean±SD)	4.8±0.71	4.79±0.71	4.69±0.71	0.245
Serum cholesterol (mg/dl) (mean±SD)	162±54.75	168.22±43.27	157.3±58.12	0.0226
Poor glycemic control, n (%)	300 (60%)	55 (55%)	245 (61.25%)	0.628
Serum albumin (g/dl) (mean±SD)	3.88±0.75	3.99±0.81	3.8±0.75	0.0627

Both the groups were similar in terms of gender, duration of diabetes, comorbidities, body mass index (BMI), blood pressure control, and glycemic control. The nonproteinuric group was older, had lesser prevalence of diabetic retinopathy ($P < 0.001$), higher hemoglobin levels and higher cholesterol levels.

Table 2: Predictors of progression of renal dysfunction (doubling of serum creatinine or requirement of dialysis)

Parameter	Outcome absent	Outcome present	P
Age (years) (mean±SD)	54.66±11.72	52.28±11.88	0.07
Females, n (%)	78 (78%)	22 (22%)	0.832
Males, n (%)	320 (80%)	80 (20%)	
Duration of diabetes mellitus (years) (mean±SD)	10.09±6.76	9.91±6.64	0.844
Hypertension, n (%)	250 (66.66%)	125 (33.34%)	0.244
CAD, n (%)	60 (80%)	15 (20%)	0.246
BMI (kg/m2) (mean±SD)	25.37±4.22	25.81±4.93	0.46
Diabetic retinopathy, n (%)	300 (85.72%)	50 (14.28%)	0.290
Cholesterol (mg/dl) (mean±SD)	161±55.23	151±53.24	0.387
Poor glycemic control, n (%) (>130/180 mg/dl)	180 (60%)	120 (40%)	0.59

We studied the predictors of progression of renal dysfunction, but no variable was found to be significantly associated with renal dysfunction.

Table 3: Predictors of the nonproteinuric phenotype by logistic regression

Parameter	Unadjusted OR	P	Adjusted OR	P
Age (years)	1.01 (0.99-1.03)	0.184	1.0 (0.99-1.03)	0.212
Females, n (%)	1.05 (0.60-1.83)	0.832	1.21 (0.65-2.26)	0.513
Duration of T2DM	0.99 (0.96-1.0)	0.636	0.99 (0.96-1.03)	0.920
Hypertension	0.80 (0.41-1.5)	0.520	0.99 (0.46-2.1)	0.942
CAD	1.51 (0.67-3.3)	0.316	1.82 (0.74-4.5)	0.190
BMI (kg/m2)	1.03 (0.98-1.08)	0.196	1.02 (0.96-1.08)	0.314
Retinopathy	0.29 (0.18-0.47)	<0.001	0.285 (0.17-0.46)	<0.001
Cholesterol (mg/dl)	1.0 (0.99-1.0)	0.052	1.0 (0.99-1.0)	0.082
Hemoglobin (g/dl)	1.22 (1.09-1.37)	<0.001	1.2 (1.06-1.36)	0.002

We applied logistic regression analysis to find predictors of nonproteinuric DKD and found that the absence of retinopathy and presence of higher hemoglobin predicted nonproteinuric phenotype.

Discussion

Kidney disease in diabetes has been classified in stages defined by increasing proteinuria and decreasing glomerular filtration rate (GFR). Classically, the development of macroalbuminuria or overt proteinuria precedes a faster decline in GFR. However, some studies have described progressive decline of GFR without significant proteinuria, i.e. nonproteinuric DKD (NP-DKD). [16,17] The understanding and growing evidence about NP-DKD led to the change in recommendation for screening of DKD based on the albumin excretion rate (AER) and estimated GFR (eGFR). Also, albuminuria has some limitation because of its intrapatient variability and the possibility of spontaneous regression, particularly in the lower level of albuminuria. [16,18] There is a continuous relationship between the level of albuminuria and the decline of GFR and cardiovascular (CV) risk. [18,19] eGFR is comparatively less variable and easily assessed in the outpatient setting.

Both the groups were similar in terms of gender, duration of diabetes, comorbidities, body mass index (BMI), blood pressure control, and glycemic control. The nonproteinuric group was older, had lesser prevalence of diabetic retinopathy ($P < 0.001$), higher hemoglobin levels and higher cholesterol levels. The study by Laranjinha et al [20] used 300 mg albumin excretion per day as the

cutoff for proteinuria. Nearly half of their study cohort (46.6%) with DKD had nonproteinuric CKD and it was more common in elderly female patients. Other studies found a prevalence of 13%–69.4% of nonproteinuric DKD. [21] There are no such data available for Indian diabetic patients. We had used a cutoff of 500 mg for proteinuria to detect proteinuric DKD (P-DKD), as this cutoff more likely reflects proteinuric disease and also is clinically significant.

We studied the predictors of progression of renal dysfunction, but no variable was found to be significantly associated with renal dysfunction. We applied logistic regression analysis to find predictors of nonproteinuric DKD and found that the absence of retinopathy and presence of higher hemoglobin predicted nonproteinuric phenotype. In the UK Prospective Diabetes Study (UKPDS-74), during 15 years of follow-up in 4,006 patients with type 2 diabetes, 1,132 (28.3%) developed renal impairment. Of the latter, 575 (50.8%) patients were classified as nonproteinuric DKD. [22] We have noted that all the patients in the current study underwent renal biopsy, which was not highly recommended in nonproteinuric DKD patients unless they were suspected of having either superimposed non-diabetic kidney disease or de novo non-diabetic kidney disease. [23] The relatively lower prevalence of nonproteinuric DN patients in the current study might be associated with the lower rate of renal biopsy in this subgroup of patients. In summary, the prevalence of nonproteinuric DKD is not low. The traditional nonproteinuric DKD should also be paid attention and concern on, mainly due to lower eGFR and renal insufficiency.

Retinopathy has been shown to be a risk marker for albuminuria, but not for decreased eGFR. Penno et al [24] demonstrated that the majority of patients with type 2 DM with diabetic retinopathy and DKD had increased albuminuria, irrespective of decreased eGFR. In our study also, the majority of patients (67.25%) had diabetic retinopathy. More patients, 218 (74.1%), in the P-DKD group had diabetic retinopathy compared to 49 (46.2%) patients in the NP-DKD group ($P < 0.001$). Hence, patients with NP-DKD may be missed as retinopathy may also be absent in this subset of population. Hypertensive retinopathy was noted in 2.38% versus 3.77% patients, respectively. In the landmark Epidemiology of Diabetes Interventions and Complications (EDIC) study, even though macroalbuminuria was the strongest predictor of worsening eGFR, screening DKD by albuminuria alone would have missed 24% of the cases with normoalbuminuric DKD. [25] Even in patients with type 1 diabetes, NP-DKD has been shown to be predictive of CV morbidity and mortality. [26,27]

Conclusion

Most patients with DKD had proteinuria, but approximately 20% had CKD without proteinuria. Simultaneous assessment of both albuminuria and eGFR is required in all diabetic patients. Studies are required to understand the utility of newer markers either alone or in combination with proteinuria to define nonproteinuric DKD.

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