Original Article

Clinical Profile of Nonproteinuric Kidney Disease in Type 2 Diabetic Patients in India

Sukhwinder Sangha, Raj Kanwar Yadav, Arunkumar Subbiah, Soumita Bagchi, Sandeep Mahajan, Dipankar Bhowmik, Sanjay Kumar Agarwal

Department of Nephrology, All India Institute of Medical Sciences (AIIMS), New Delhi, India

Abstract

Background: Diabetic kidney disease (DKD) is the commonest cause of end-stage renal disease (ESRD) across the world. Development of microalbuminuria is the earliest marker of DKD and predicts progressive decline in estimated glomerular filtration rate (eGFR). However, recent evidence has suggested that a significant proportion of type 2 diabetic patients have chronic kidney disease (CKD) without proteinuria. **Methods:** In this single-center, prospective observational study, 400 consecutive type 2 diabetic patients with either overt proteinuria (>500 mg/day) and/or renal dysfunction eGFR <60 ml/min/1.73 m^2) were recruited. Baseline demographic and clinical data were recorded. eGFR and proteinuria were recorded at 6 months and 1 year. Patients with proteinuric (proteinuria >0.5 g/day) and nonproteinuric phenotypes were compared for progression of renal dysfunction in terms of doubling of serum creatinine and need for dialysis. **Results:** In our study cohort, 106 (26.5%) were nonproteinuric. 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 (56.5 ± 2.1 vs. 54.7 ± 11.6 years, P = 0.012), had lesser prevalence of diabetic retinopathy (49 [46.2%] vs. 218 [74.1%], P < 0.001), higher hemoglobin levels (11.3 ± 1.7 vs. 10.5 ± 2.0 g/dl, P < 0.001), and higher cholesterol levels (169.3 ± 43.3 vs 157.1 ± 58.1 mg/dl, P = 0.025). The nonproteinuric phenotype had higher eGFR at baseline, 6 months, and 1 year. However, doubling of serum creatinine (10 [9.4%] vs. 48 [16.3%]) and progression to ESRD (5 [4.7%] vs. 19 [6.5%], P = 0.159) were not different between the two phenotypes. **Conclusion:** Nonproteinuric DKD is common. Patients with nonproteinuric DKD tend to be older with a slower decline in eGFR.

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. 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.[1] 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).[2,3] Although the decline in GFR can occur in the absence of proteinuria, the development of advanced CKD classically follows overt proteinuria.[4] 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.[5] 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.[2,6] There is a continuous relationship between the level of albuminuria and the decline of GFR and cardiovascular (CV) risk.[6,7] eGFR is comparatively less variable and easily assessed in the outpatient setting. Reports from western countries suggest that the prevalence of NP-DKD ranges from 20% to 40%.[8] In spite of this high prevalence, data regarding the clinical characteristics of these patients are lacking. This leads to insufficient knowledge about treating

How to cite this article: Sangha S, Yadav RK, Subbiah A, Bagchi S, Mahajan S, Bhowmik D, *et al.* Clinical profile of nonproteinuric kidney disease in type 2 diabetic patients in India. Indian J Nephrol 2023;33:283-8.

Received: 09-02-2022
Revised: 15-09-2022
Accepted: 19-10-2022
Published: 04-04-2023

Address for correspondence:
Dr. Raj Kanwar Yadav, Department of Nephrology, Room No 4087, 4th Floor, Teaching Block, AIIMS, New Delhi - 110 029, India.
E-mail: rkyadavnephrology@gmail.com

Access this article online

Website: https://journals.lww.com/ijon

DOI: 10.4103/ijn.ijn_54_22

Quick Response Code:

this subgroup of patients as they are often excluded from the classic DKD trials. The very existence, prevalence, and clinical profile of this NP-DKD phenotype are not well defined, more so in the Indian population. This study aims to evaluate the demographic and clinical characteristics of NP-DKD in type 2 diabetic Indian patients.

Materials and Methods

This study was a single-center, prospective cohort study conducted in the Department of Nephrology at the All India Institute of Medical Sciences, New Delhi, between Sept 2018 and Dec 2019. Written and informed consent was sought from all participants. Type 2 diabetic patients of more than 18 years age with either proteinuria >500 mg/day and/or renal dysfunction (e-GFR <60 ml/min/1.73 m^2) were included in the study. 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 m^2 (not all had eGFR <60 ml) or proteinuria greater than 500 mg/day were divided into two groups: proteinuric and nonproteinuric. 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.

The required sample size was estimated to be 364 patients to provide a power of 80% and an α of 0.05 for detecting approximately 40% prevalence of nonproteinuric kidney disease in T2 diabetic patients, as shown in earlier studies. 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

Among our study cohort of 400 patients, 106 (26.5%) patients were in the nonproteinuric (NP-DKD) group. The baseline characteristics of patients are shown in Table 1. Mean proteinuria at baseline was 2.1 ± 2.4 g/g, at 6 months was 2.0 ± 2.1 g/g, and at 1 year was 2.0 ± 2.2 g/g. Mean creatinine at baseline was 2.2 ± 1.0 mg/dl, at 6 months was 2.6 ± 1.5 mg/dl, and at 1 year was 3.0 ± 1.9 mg/dl. At baseline, male patients had higher eGFR (42.7 ± 23.8 ml/min/1.73m^2) when compared to females (34.7 ± 15.8 ml/min/1.73m^2). The mean eGFR at baseline was 41.2 ± 22.7 ml/min/1.73 m^2, at 6 months was 35.7 ± 19.4 ml/min/1.73 m^2, and at 1 year was 33.5 ± 31.1 ml/min/1.73m^2 [Figure 1]. There was a progressive fall in eGFR during follow-up. There was no difference in eGFR between nonproteinuric and proteinuric groups at baseline (42.9 ± 19.32 vs. 40.6 ± 23.8 ml/min/1.73 m^2, $P = 0.33$); however, at follow-up of 6 months (41.6 ± 19.9 vs. 33.7 ± 18.8 ml/min/1.73 m^2, $P < 0.001$) and 1 year (44.5 ± 51.59 vs. 33.6 ± 31.1 ml/min/1.73 m^2, $P = 0.004$), patients in the nonproteinuric group had significantly higher eGFR [Figure 1]. We found that there was a significant difference in fall of eGFR during 1 year of follow-up between the two phenotypes; eGFR was less in the proteinuric group by 5.7 ± 2.4 ml/min/1.73 m^2 at 6 months and 12.7 ± 2.8 ml/min/1.73 m^2 at 1 year.

Progression of renal dysfunction was studied in terms of no change, doubling of serum creatinine, and need for RRT. We found that 79.5% of patients had no change, 14.5% had doubling of serum creatinine, and 6% required RRT during the follow-up at the end of 1 year. Although the doubling of serum

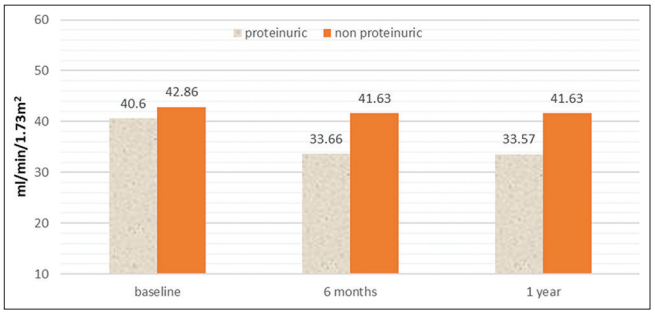

Figure 1: Trend of renal function in patients with proteinuric and non-proteinuric diabetic kidney disease

creatinine and RRT requirement was more in the proteinuric phenotype, this difference was not statistically significant.

We studied the status of proteinuria during follow-up. No change in proteinuria was seen in 48.75% of patients, 50% decrease in proteinuria was found in 10.75% of patients, and 50% increase in proteinuria was found in 14.75% of patients. More patients, 162 (55.1%), in the proteinuric phenotype compared to 31 (29.25%) patients in the nonproteinuric phenotype were on ACE-i/ARB therapy. We studied the predictors of progression of renal dysfunction, but no variable was found to be significantly associated with renal dysfunction [Table 2]. Renal biopsy was advised to all patients with atypical features suggesting other alternative diagnoses to DKD. Nineteen patients underwent kidney biopsy. Six patients had DKD on biopsy, four had mixed lesions, and nine patients had an alternative diagnosis, as shown in Figure 2.

We applied logistic regression analysis to find predictors of nonproteinuric DKD [Table 3] and found that the absence of retinopathy and presence of higher hemoglobin predicted nonproteinuric phenotype.

Discussion

NP-DKD is a less common but clinically significant cause of progressive renal dysfunction in diabetic patients.[9] Clinical characteristics differentiating proteinuric from nonproteinuric phenotypes ensure timely diagnosis and prognostication. The study by Laranjinha *et al.*[8] 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.[10] There are no such data available for Indian diabetic patients. We had used a cutoff of 500 mg for proteinuria to detect proteinuric

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

Parameter	All patients (*n*=400)	Nonproteinuric (*n*=106)	Proteinuric (*n*=294)	*P*
Age (in years) (mean±SD)	55.15±11.78	56.47±12.08	54.68±11.65	0.0128
Males, *n* (%)	323 (80.75%)	85 (80.18%)	238 (80.95%)	0.864
Duration of diabetes mellitus (years), median (range)	10 (5-15)	9.81±7.05	10.15±6.62	0.5370
Hypertension, *n* (%)	284 (71%)	68 (64.15%)	216 (73.47%)	0.180
CAD, *n* (%)	62 (15.5%)	23 (21.70%)	39 (13.27%)	0.180
CVA, *n* (%)	4 (1%)	1 (0.94%)	3 (1.02%)	0.180
BMI (kg/m^2) (mean±SD)	25.46±4.37	25.93±4.60	25.29±4.28	0.195
Blood pressure control (>140/90 mmHg), *n* (%)	81 (20.85%)	15 (14.15%)	66 (22.45%)	0.068
Diabetic retinopathy, *n* (%)	269 (67.25%)	49 (46.23%)	218 (74.15%)	<0.001
Hemoglobin (g/dl) (mean±SD)	10.7±2	11.32±1.96	10.47±2.02	<0.001
Serum albumin (g/dl) (mean±SD)	3.88±0.75	3.99±0.81	3.80±0.75	0.0654
eGFR (ml/min/1.73 m^2) (mean±SD)	41.20±22.72	42.86±19.32	40.6±23.83	0.3345
Serum potassium (mEq/dl) (mean±SD)	4.7±0.71	4.77±0.71	4.68±0.71	0.290
Serum cholesterol (mg/dl) (mean±SD)	160±54.82	169.26±43.28	157.1±58.15	0.0253
Poor glycemic control, *n* (%)	230 (57.5%)	59 (55.66%)	171 (58.16%)	0.655
Serum albumin (g/dl) (mean±SD)	3.88±0.75	3.99±0.81	3.8±0.75	0.0654

SD=Standard deviation

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)	55.65±11.72	53.24±11.89	0.09
Females, *n* (%)	60 (77.9%)	17 (22.07%)	0.864
Males, *n* (%)	258 (79.8%)	65 (20.12%)	
Duration of diabetes mellitus (years) (mean±SD)	10.09±6.76	9.96±6.64	0.887
Hypertension, *n* (%)	206 (65.5%)	50 (60.97%)	0.288
Hypertension+CAD, *n* (%)	28 (8.8%)	6 (7.3%)	0.288
ACE-i/ARB use, *n* (%)	149 (46.85%)	44 (53.65%)	0.165
BMI (kg/m^2) (mean±SD)	25.37±4.22	25.81±4.93	0.46
Poor blood pressure control (>140/90 mmHg), *n* (%)	59 (18.55%)	22 (26.82%)	0.096
Diabetic retinopathy, *n* (%)	218 (69.64%)	62 (75.6%)	0.290
Cholesterol (mg/dl) (mean±SD)	161±55.23	151±53.24	0.387
Poor glycemic control, *n* (%) (>130/180 mg/dl)	185 (58.17%)	45 (54.8%)	0.59

BMI=Body mass index, SD=Standard deviation

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)	0.181	1.0 (0.99-1.03)	0.210
Females, *n* (%)	1.05 (0.60-1.83)	0.864	1.21 (0.65-2.26)	0.531
Duration of T2DM	0.99 (0.96-1.0)	0.661	0.99 (0.96-1.03)	0.915
Hypertension	0.80 (0.41-1.5)	0.539	0.99 (0.46-2.1)	0.984
CAD	1.51 (0.67-3.3)	0.310	1.82 (0.74-4.5)	0.190
BMI (kg/m^2)	1.03 (0.98-1.08)	0.195	1.02 (0.96-1.08)	0.397
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)	0.053	1.0 (0.99-1.0)	0.083
Hemoglobin (g/dl)	1.22 (1.09-1.37)	<0.001	1.2 (1.06-1.36)	0.002

BMI=Body mass index, OR=Odds ratio, T2DM=Type 2 diabetes mellitus

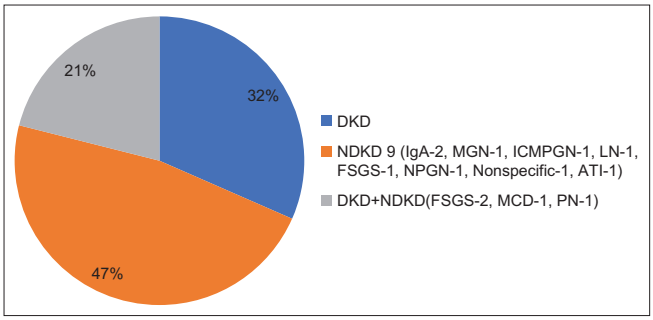

Figure 2: Spectrum of renal biopsy findings in patients with diabetes mellitus

DKD (P-DKD), as this cutoff more likely reflects proteinuric disease and also is clinically significant. In our study, 26.5% of patients were nonproteinuric (NP-DKD group). This proportion is comparable to studies[11] done in other countries, and the difference in prevalence in different studies is most likely due to varying proteinuria cutoffs used.

The NEFRON study found that nonalbuminuric patients were older and more frequently females.[12] Older age is a risk factor not only for lower eGFR, but also for higher albuminuria. The female preponderance for nonalbuminuric DKD (NA-DKD) is seen in other studies also. The NDR and UKPDS studies have shown female gender as a risk factor for renal impairment (GFR ≤60 ml/min) and male gender for the development of albuminuria.[13] In our study population, only 19.25% were females. The proteinuric and nonproteinuric phenotypes had equal gender distribution. The absence of female predominance in our study was probably due to overall lesser number of females in our study. It probably also reflects less access to health care for females in our society. The nonproteinuric phenotype was a little older than the proteinuric phenotype (56.47 ± 12.08 vs. 54.68 ± 11.65 years, *P* = 0.012), which is consistent with previous studies.

In the NEFRON study, NA-DKD patients had more advanced CKD with lower eGFR and lower hemoglobin than patients with albuminuric DKD (A-DKD). In our study, both phenotypes had a similar baseline eGFR; however, at follow-up of 6 months (41.6 ± 19.95 vs. 33.7 ± 18.8 ml/min/1.73 m^2, *P* = 0.0003) and 1-year (44.5 ± 51.6 vs. 33.6 ± 31.09, *P* = 0.004) time points, the nonproteinuric group had significantly higher eGFR. By multivariate analysis, we found that e-GFR was significantly lower in the proteinuric phenotype by 5.7 ± 2.4 ml/min/1.73 m^2 at 6 months and 12.7 ± 2.8 ml/min/1.73 m^2 at 1 year. The nonproteinuric phenotype had higher mean hemoglobin (11.3 ± 1.9 vs. 10.4 ± 2.0 g/dl, *P* < 0.001) and higher mean serum cholesterol (169.3 ± 43.3 vs. 157.1 ± 58.1 mg/dl, *P* = 0.0253).

The cause of renal dysfunction in NA-DKD patients is proposed to be due to macroangiopathy, interstitial disease, and reduced renal mass, rather than glomerulopathy.[14] They also found that metabolic syndrome prevalence was not different between albuminuric and nonalbuminuric patients; however, they noted a tendency of a higher prevalence of some metabolic syndrome criteria, such as hypertension, dyslipidemia, and hypertriglyceridemia, in the albuminuric group. In our study, mean BMI was comparable between the two groups (25.9 ± 4.6 vs. 25.3 ± 4.3 kg/m^2, *P* = 0.195). The NP-DKD group had similar prevalence of hypertension (68 [64.15%] vs. 216 [73.47%]), Coronary artery disease (CAD) (23 [21.70%] vs. 39 [13.3%]), and cerebrovascular accident (CVA)(1 [0.94%] vs. 3 [1.0%]) as that of P-DKD group. The nonproteinuric phenotype had higher hemoglobin concentration (11.32 ± 1.96 vs. 10.47 ± 2.02 g/dl, *P* < 0.001) and higher serum cholesterol (169.3 ± 43.3 vs. 157.1 ± 58.1 mg/dl, *P* = 0.0253). The study that analyzed the prevalence of metabolic syndrome in NA-DKD found it to be more frequent in nonalbuminuric patients. Other studies found variable results concerning the prevalence of isolated metabolic syndrome. It remains unclear why some patients develop DKD with significant albuminuria, while others have impaired renal function without albuminuria. NA-DKD can be due to hypertensive nephron angiosclerosis, which is the second main cause of CKD in developed countries. However, in our study, hypertension prevalence was similar between the groups. It can also be suggested that renin angiotensin system (RAS) blockade can suppress albuminuria and can explain the nonproteinuric

phenotype. Such patients could not be excluded from our study. In our patients, the metabolic control of diabetes was also not different between the two groups. The UKPDS study did show that higher glycated hemoglobin (HbA1c) is a predictor for albuminuria, but not for decreased GFR.[15] We could not use HbA1c criteria because of logistic issues and also due to the fact that it may also be unreliable in patients with a moderate degree of renal impairment.

Retinopathy has been shown to be a risk marker for albuminuria, but not for decreased eGFR. Penno *et al.*[16] 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.

Even patients with type 1 diabetes can have DKD without proteinuria. 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.[17] Even in patients with type 1 diabetes, NP-DKD has been shown to be predictive of CV morbidity and mortality.[18]

There are limited studies comparing renal biopsy findings in NA-DKD and A-DKD patients. There is no classic histopathologic finding for the nonalbuminuric phenotype. Porrini *et al.*[14] showed that NA-DKD patients had a rate of GFR decline of 3.5 ml/min/1.73 m^2, and that A-DKD patients had an even higher decline of GFR. In our study, progression of renal dysfunction was studied in terms of no change, doubling of serum creatinine, and need of dialysis. The majority (79.5%) of the patients had no change, 14.5% had doubling of serum creatinine, and 6% progressed to dialysis-requiring stage during the follow-up period of 1 year. However, no difference was found between the two groups. We also studied the status of proteinuria in the follow-up of 1 year on two occasions. No change in proteinuria was seen in 48.75% of patients. In 17.75%, proteinuria regressed to less than 500 mg/day, and in 8%, it progressed to more than 500 mg/day. Also, a 50% decrease in proteinuria was seen in 10.75% and a 50% increase in proteinuria was seen in 14.75% of patients. We also compared the progression of proteinuria in the two phenotypes. About 71 (24.14%) patients in P-DKD showed regression of proteinuria, while 32 (30.19%) patients in NP-DKD showed progression of proteinuria. 19 (17.92%), in P-DKD versus 24 (8.16%) in NP-DKD showed 50% decrease in proteinuria; also, more patients, 48 (16.33%), in NP-DKD versus 11 (10.38%) in P-DKD showed 50% increase in proteinuria.

As proteinuria is the only known clinical marker of DKD till date, newer markers are required to screen for nonproteinuric DKD. One such marker, the CKD273 classifier, a proteomic biomarker, has shown promise for diagnosing NP-DKD.[19] Albuminuria is an important predictor of CV events in diabetic patients. In NP-DKD, it has been shown that renal function as assessed by eGFR predicts CV events and needs to be monitored.[20] It should be remembered that absence of albuminuria does not negate CV risk and mortality in DKD.

The strengths of our study are the sample size, the real-world observation of study variables, and absence of patient dropouts. Apart from the inherent drawbacks of observational studies, limitations of our present study include higher cutoff value of proteinuria, a shorter duration of follow-up, and lack of histological confirmation of the nature of kidney disease.

Conclusion

Most patients with DKD had proteinuria, but approximately one fourth (26.5%) 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.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. KDOQI. KDOQI clinical practice guidelines and clinical practice recommendations for diabetes and chronic kidney disease. Am J Kidney Dis 2007;49(Suppl 2):S12-154.
2. Herman WH, Zimmet P. Type 2 diabetes: An epidemic requiring global attention and urgent action. Diabetes Care 2012;35:943-4.
3. Halimi JM. The emerging concept of chronic kidney disease without clinical proteinuria in diabetic patients. Diabetes Metab 2012;38:291-7.
4. Weil EJ, Fufaa G, Jones LI, Lovato T, Lemley KV, Hanson RL, *et al.* Effect of losartan on prevention and progression of early diabetic nephropathy in American Indians with type 2 diabetes. Diabetes 2013;62:3224-31.
5. Chawla V, Roshan B. Non-proteinuric diabetic nephropathy. Curr Diab Rep 2014;14:529.
6. Perkins BA, Ficociello LH, Silva KH, Finkelstein DM, Warram JH, Krolewski AS. Regression of microalbuminuria in type 1 diabetes. N Engl J Med 2003;348:2285-93.
7. Gall MA, Nielsen FS, Smidt UM, Parving HH. The course of kidney function in type 2 (non-insulin-dependent) diabetic patients with diabetic nephropathy. Diabetologia 1993;36:1071-8.
8. Laranjinha I, MAtias P, Mateus S, Aguiar F, Pereira P, Perneta Santos M, *et al.* Diabetic kidney disease: Is there a non-albuminuric phenotype in type 2 diabetic patients?

Nefrologia 2016;36:503-9.
9. Ritz E, Orth SR. Nephropathy in patients with type 2 diabetes mellitus. N Engl J Med 1999;341:1127-33.
10. Yamanouchi M, Furuichi K, Hoshino J, Ubara Y, Wada T. Nonproteinuric diabetic kidney disease. Clin Exp Nephrol 2020;24:573-81.
11. Kramer HJ, Nguyen QD, Curhan G, Hus C-Y. Renal insufficiency in the absence of albuminuria and retinopathy among adults with type 2 diabetes mellitus. JAMA 2003;289:3273-7.
12. Thomas MC, Macisaac RJ, Jerums G, Weekes A, Moran J, Shaw JE, *et al.* Nonalbuminuric renal impairment in type 2 diabetic patients and in the general population (national evaluation of the frequency of renal impairment cO-existing with NIDDM [NEFRON] 11). Diabetes Care 2009;32:1497-502.
13. Afghahi H, Cederholm J, Eliasson B, Zethelius B, Gudbjörnsdottir S, Hadimeri H, *et al.* Risk factors for the development of albuminuria and renal impairment in type 2 diabetes—the Swedish National Diabetes Register (NDR). NDT 2011;26:1236-43.
14. Porrini E, Ruggeneti P, Mogensen CE, Barlovic DP, Praga M, Cruzado JM, *et al.* Non-proteinuric pathways in loss of renal function in patients with type 2 diabetes. Lancet Diabetes Endocrinol 2015;3:382-91.
15. Retnakaran R, Cull CA, Thorne KI, Adler AI, Holman RR, UKPDS Study group. Risk factors for renal dysfunction in type 2 diabetes: UK prospective diabetes study 74. Diabetes 2006;55:1832-9.
16. Penno G, Solini A, Zoppini G, Orsi E, Zerbini G, Trevisan R, *et al.* Rate and determinants of association between advanced retinopathy and chronic kidney disease in patients with type 2 diabetes: The renal insufficiency and cardiovascular events (RIACE) Italian multicenter study. Diabetes Care 2012;35:2317-23.
17. Molitch ME, Steffes M, Sun W, Rutledge B, Cleary P, de Boer IH, *et al.* Development and progression of renal insufficiency with and without albuminuria in adults with type 1 diabetes in the diabetes control and complications trial and the epidemiology of diabetes interventions and complications study. Diabetes Care 2010;33:1536-43.
18. Thorn LM, Gordin D, Harjutsala V, Hägg S, Masar R, Saraheimo M, *et al.* The presence and consequence of nonalbuminuric chronic kidney disease in patients with type 1 diabetes. Diabetes Care 2015;38:2128-33.
19. Zoccali C, Mallamaci F. Nonproteinuric progressive diabetic kidney disease. Curr Opin Nephrol Hypertens 2019;28:227-32.
20. Svensson MK, Cederholm J, Eliasson B, Zethelius B, Gudbjörnsdottir S; Swedish National Diabetes Register. Albuminuria and renal function as predictors of cardiovascular events and mortality in a general population of patients with type 2 diabetes: A nationwide observational study from the Swedish National Diabetes Register. Diab Vasc Dis Res 2013;10:520-9.