Original Article

Prevalence of Diabetic Kidney Disease and Its Associated Risk Factors in Type-2 Diabetes Mellitus — A Tertiary Care Experience

Shaila Jay Shah[1], Jay Harishbhai Shah[2], Parth Prajapati[3]

Background : The burden of diabetes is increasing in India with its associated complications. Diabetic Kidney Disease (DKD) is one of the microvascular complications of Diabetes Mellitus (DM) which leads to End Stage Renal Disease (ESRD). Regional and ethnic differences have been noted globally and within India regarding diabetes, its risk factors and its ensuing complications. DKD is identified clinically by a persistently elevated Urine Albumin/Creatine Ratio (UACR) of >30mg/g and/or a persistently decreased eGFR below 60 ml/min/1.73m^2.

Materials and Methods : This was a single centre cross-sectional observational study which included 150 patients. All patients with known type 2 diabetes or newly diagnosed diabetes presenting to the Department of Medicine for the first time were included after screening and fulfilling the said inclusion and exclusion criteria. Primary objectives were to estimate the prevalence of DKD in type 2 diabetes mellitus and to determine the CKD stage of patients with DKD. Secondary objectives were to determine the association of various risk factors with DKD and to determine correlation between UACR and HbA1c, e-GFR and serum creatinine.

Results : DKD was found in 111(74%) of patients. 99(66%) of patients had hypertension, 81 of whom had DKD. There were 59(39.33%) patients with stage G2 and 58(38.67%) in stage G3 out of which 34 patients were in stage G3a and 24 were in G3b. Fifty (33.33%) patients had A1, 89(59.33%) patients had A2 and 11(7.34%) had A3 stages of albuminuria. Presence of hypertension, retinopathy and duration of DM were found to have a significant association with DKD prevalence. Hypertension also had a significant negative correlation with eGFR.

Conclusion : The prevalence of DKD in the population may be under-estimated. It remains imperative to detect and control diabetes early and treat associated risk factors like hypertension diligently to delay the occurrence and progression of DKD.

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Key words **: Diabetes, Kidney Disease, Hypertension, Prevalence, Stages of CKD.**

The burden of diabetes is increasing in India as well as globally. It has been estimated that India had 77 million diabetics in 2019, 57% of which supposedly remain undiagnosed[1]. It is expected that by 2030 and 2045, India shall have 101.0 and 134.2 million diabetics respectively surpassed only by China[2]. Regional differences are found across various states in India itself owing to cultural and genetic differences[3]. According to the ICMR-INDIAB study 9.5% of urban and 5.1% of rural population was found to have diabetes in the state of Gujarat while it ranged from 3.5%-8.7% in rural and 5.8-15.5% in urban population across the country[4]. This highlights the need to carry out various studies related to diabetes at regional levels to help manage diabetes and its various complications in a better manner.

Department of General Medicine, GCS Medical College, Hospital and Research Centre, Ahmedabad, Gujarat 380025
[1]MD, Associate Professor and Corresponding Author
[2]MD, Senior Resident
[3]MBBS, Junior Resident

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Editor's Comment :

- The prevalence of diabetic nephropathy may be higher than expected in the population.
- Hypertension needs to be diligently controlled in all diabetic patients.
- Early detection of nephropathy needs to be encouraged and measures taken to halt its progression in these patients.

Diabetes Mellitus (DM) is known to have microvascular and macrovascular complications out of which Diabetic Kidney Disease (DKD) is one of the microvascular complications leading to End Stage Renal Disease (ESRD). The clinical diagnosis of DKD is done on the basis of measurement of estimated glomerular filtration rate (eGFR) and the presence of albuminuria. It is identified clinically by a persistently elevated urine albumin/creatine ratio (UACR) of >30mg/g and/or a persistently decreased eGFR below 60 ml/min/1.73m^2. The urinary albumin to creatine ratio done on a spot urine sample preferably a morning sample is the preferred test for albuminuria. Two measurements of atleast 3 months apart, of eGFR and albuminuria are required to confirm the diagnosis of DKD[5].

It has been reported that 80% cases of ESRD globally are due to either diabetes or hypertension[6]. Two studies, one from United States and India each, found that 44% of patients with ESRD were due to Diabetes Mellitus[7-8]. However, the prevalence of diabetes and its complications vary as per regional and ethnic differences as demonstrated by various studies. In a cross-sectional study involving 32,208 type 2 diabetics without known albuminuria across 33 countries, it was found that the Asian-Hispanic population had the highest prevalence of a raised urine albumin/creatine ratio at 55% and Caucasians had the lowest at 40.6%[9]. It is estimated that 25% of diabetics in the United Kingdom and 36% of diabetics in the United States have diabetic nephropathy[10]. In a systematic review done for 32 countries of Africa, the incidence of DKD disease varied between 11 to 83.7%[11].

In the START-INDIA study, performed at 30 different sites and having 3000 subjects the prevalence of DKD was found to be 48.4%[12]. In another study, involving two centres the prevalence of DKD was found to be 62.3%[13]. In a study of 100 newly diagnosed type 2 diabetic patients, the prevalence of DKD was found to be 43%[14]. Owing to the increasing prevalence of type 2 diabetes in India and a paucity of national data on the prevalence of DKD, we decided to conduct a study regarding diabetic kidney disease in type 2 diabetes attending our institution.

Materials and Methods

Study Type :

This was a single centre observational cross-sectional study conducted at a Tertiary Care Hospital in Ahmedabad carried during the period of September, 2019 to August, 2021 after getting the approval by the Institutional Ethics Committee vide no. GCSMC/EC/Dissertation/APPROVE/2019/0066.

Study Objectives :

Primary objective

- To estimate the prevalence of DKD in type 2 diabetes mellitus at our institution
- To determine the CKD stage of patients with DKD.

Secondary objectives

- To determine the association of various risk factors with DKD
- To determine correlation between UACR and HbA1c, e-GFR and serum creatinine

Study Population :

All patients with known type 2 diabetes or newly diagnosed diabetes presenting to the Department of Medicine for the first time were included after screening and fulfilling the said inclusion and exclusion criteria. All patients who participated gave prior consent for enrolment in the study.

Inclusion Criteria :

- Patients with Type 2 Diabetes Mellitus (DM) of age equal to more than 18 years.

Exclusion Criteria :

- Patients with Type 1 DM
- Patients not willing to get enrolled in the study
- Patients with non-diabetic kidney disease
- Patients on maintenance dialysis
- Patients with urinary tract infection
- Patients with obstructive uropathy
- Patients presenting with acute febrile illness
- Other acute illnesses
- Cancer patients
- Pregnant patients
- Patients on steroids

Data Collection :

Demographic data in the form of age and gender, data regarding co-morbid illness like hypertension and IHD, family history, habits of the patients etc. was recorded. Duration of diabetes and treatment details of patients were also noted. Vital data in the form of blood pressure and Body Mass Index (BMI) were noted. Laboratory investigations were carried out and recorded. All patients underwent fasting and post-prandial blood glucose, glycosylated hemoglobin, serum creatinine level, ultrasound of kidney, echocardiography and fundus examination were carried out and recorded.

A single spot morning sample of urine for collected and UACR calculated by the immunoturbidometric method. eGFR was calculated with the help of Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. The tests were repeated after three to six month sunless the patients had previous records regarding the same. The latest results were considered for study purposes. DKD was diagnosed and classified as per KDIGO 2012 classification[15]. Patients were classified as per the albuminuria as A1(mildly increased), A2(moderately increased) and A3(severely increased) as per KDIGO 2012 guidelines. Patients were said to be hypertensive if patients were already on medication for hypertension or previously had been on treatment for hypertension. For newly diagnosed hypertensives, two random office measurements in sitting position were recorded and a mean of both readings was taken. Patients were considered to be

hypertensive if either Systolic Blood Pressure (SBP) was above 140 mm Hg or Diastolic Blood Pressure (DBP) was above 90 mm Hg. Diabetes Mellitus (DM) was diagnosed as per latest guidelines of ADA[16]. HbA1c of more than 7.0% was considered as uncontrolled diabetes. Patients were classified as normal, overweight or obese as per the Indian consensus guidelines[17].

Statistical Analysis :

Categorical data was analysed using proportions and percentages. Chi-square test was used for analysis for single variables and multivariable logistic regression was used for studying the association of DKD with multiple variables. The Hosmer-Lemeshow model for goodness of fit was used. Continuous data was analysed in the forms of mean and Standard Deviation (SD). The Pearson's correlation coefficient was utilised to study the association between continuous variables. The two-tailed Student's t-test was utilised where required. Limits were set at 95% confidence intervals and $p<0.05$ was considered statistically significant.

Results

During the study period a total of 362 patients were screened for the eligibility of the study out of which 218 patients were found eligible. Finally, 150 patients could be a part of the study as 68 patients were lost to follow-up.

Demographic Data :

The study population comprised of 85(56.67%) females and 65(43.43%) males. The M:F ratio in our study was 0.76. The mean age, BMI, duration of diabetes, FBS, PPBS HbA1c, creatinine, eGFR and UACR are depicted in Table 1. Eighty-one patients (54%) had normal creatine levels while 69 (46%) patients had raised creatinine levels. (upper limit of normal for S.creatinine being 1.2 mg/dl). HbA1c was more than 7% in 120(80%) patients while 30(20%) patients had a HbA1c of less than or equal to 7%.

Primary Objectives :

Prevalence of DKD.

DKD was found to be present in 111 of the study participants and the prevalence of DKD was 74% in our study.

Prevalence of Various CKD Stages :

The prevalence of various CKD stages is shown in Table 2. There were 59(39.33%) patients with stage G2 and 58(38.67%) in stage G3 out of which 34 patients were in stage G3a and 24 were in G3b. Fifty (33.33%) patients had A1, 89(59.33%) patients had A2 and 11(7.34%) had A3 stages of albuminuria. Out of the 89 patients in A2 category 77(86.5%) patients were in stages G2 and G3 combined. Out of the 150 patients almost half (77 patients, 51.33%) were in category A2, G2 or G3 staging of CKD. As far as risk of progression of CKD was concerned, 38(25.33%) were at mildly increased risk, 45(30%) were at moderately increased risk, 27(18%) were at high risk and 40(26.67%) were at very high risk of disease progression.

Table 1 — *Demographic and Laboratory parameters of study participants*

Parameters	Mean (SD)
Age (years)	56.5(11.38)
BMI (kg/m^2)	26.16(3.76)
DM duration(years)	10.34(7.13)
FBS (mg/dl)	179.9(67.75)
PPBS (mg/dl)	272.97(88.11)
HbA1c (%)	9.23(2.37)
Creatinine (mg/dl)	1.38(0.62)
eGFR(ml/min/1.73m^2)	59.54(23.93)
UACR (mg/g)	86.76(99.20)

Secondary Objectives :

Risk factors associated with DKD

Age and Gender :

The mean (SD) age of our study patients was 56.5(11.38) years. One hundred twenty-four(82.67%) of patients were between the age group of 41 and 70 years. Out of 111 patients with DKD, 73(65.76%) belonged to the age group between 51 to 70 years. (Fig 1). There were only 12 patients in the age group

Table 2 — *Prevalence of various CKD stages and distribution and risk of progression of study participants as per KDIGO 2012*

Prognosis of CKD by GFR and albuminuria categories:KDIGO 2012		Persistent albuminuria/ proteinuria categories (description and range)			
GFR categories	eGFR ml/min/1.73m^{-2}	A1<30mg/g Normal to mildly increase	A2 30-299mg/g moderately increased	A3≥300mg/g severely increased	Total (%)
G1	**≥90**	**15(10)**	**2(1.33)**	**0(0)**	**17(11.33)**
G2	**60-90**	**23(15.33)**	**33(22)**	**3(2)**	**59(39.33)**
G3a	**45-59**	**10(6.67)**	**22(14.67)**	**2(1.33)**	**34(22.67)**
G3b	**30-44**	**2(1.33)**	**23(15.33)**	**0(0)**	**25(16.67)**
G4	**15-29**	**0(0)**	**9(6)**	**4(2.67)**	**13(8.67)**
G5	**<15**	**0(0)**	**1(0.67)**	**1(0.67)**	**2(1.33)**
	Total (%)	**50(33.33)**	**90(60)**	**10(6.67)**	**150(100)**

Green : Low risk (if no other marker of kidney disease, no CKD);
Yellow : moderately increased risk; **Orange :** high risk; **Red :** very high risk.

of 71-90 years of which 9(75%) patients had DKD as opposed to 50 out of which 29(58%) had DKD in the age group of 31-50 years and 88 out of which 70(79.54%) had DKD in the age group of 51-70 years.

We found that this difference in the prevalence of DKD was statistically significant (χ^2=7.39, p=0.02), however, it failed to show significance on multivariable regression analysis (Table 3).

In our study we found a predominance of female gender as previously mentioned however, we did not find a significant association between gender and the prevalence of DKD in our study (Table 4).

Blood Pressure :

Ninety-nine (66%) of patients in our study were hypertensive out of which 81 patients had DKD and they comprised 72.97% of the patients having DKD. Presence of hypertension was significantly associated with DKD on both univariable analysis and multivariable logistic regression analysis. The mean (SD) duration of hypertension was 9(5.90) years. There was no significant correlation found between the duration of hypertension and UACR (R=-0.0314, p=0.75) or eGFR (R=-0.1632, p=0.10). The UACR between the hypertensive and normotensive group showed no significant difference of means (t=1.210, p=0.229) but a significant difference was noted in the eGFR between the normotensive and hypertensive groups (t=-2.744,p=0.007).

Body Mass Index (BMI) :

There were 90(60%) patients in the obese category and 30(20%) patients each in the normal and overweight categories. There was no significant difference noted in the prevalence of DKD within the three groups (Table 4).

Duration of Diabetes Mellitus :

The maximum number of patients, 45(30%) in our study had a duration of diabetes of less than five years. Twelve (8%) patients had newly diagnosed diabetes(<6 months), out of which five(41.67%) patients had DKD. We found that the duration of diabetes had a significant effect on the prevalence of DKD both by univariable and multivariable regression analysis.

Diabetic Retinopathy :

Forty-two (28%) of the study patients were found

Table 3 — *Multivariable logistic regression for factors influencing the prevalence of DKD*

Variable	β-Coefficient	Standard Error	p-value	Odds Ratio	95% Confidence Interval
Hypertension	1.1347	0.5228	0.03	3.1102	(1.1162, 8.6660)
DM duration	1.4243	0.5551	0.0103	4.1548	(1.3999, 12.3313)
Retinopathy	0.0209	0.6012	0.9723	1.0211	(0.3143, 3.3174)
Age	-0.0206	0.0258	0.425	0.9796	(0.9313, 1.0305)
Gender	-0.2553	0.5303	0.6302	0.7747	(0.2740, 2.1903)
HbA1c	-0.0739	0.1063	0.4869	0.9288	(0.7542, 1.1438)
Constant	-0.3693	2.1309	0.8624		
Chi-Square=17.3268, df=6, p-value= 0.0082 (Model of goodness of fit)					

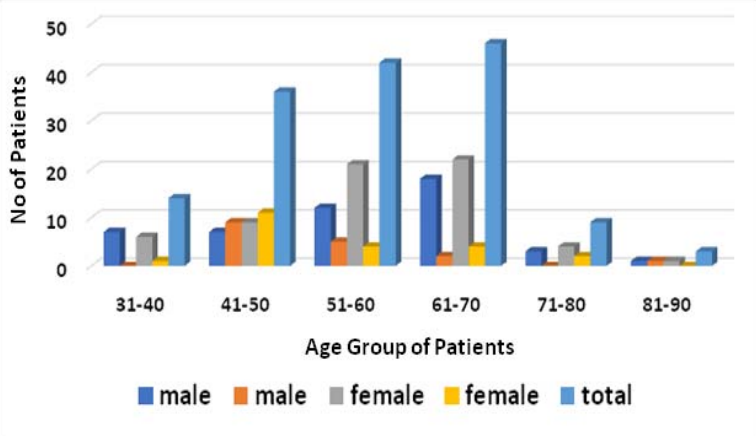

Fig 1 — Age and Gender distribution of participants with and without DKD

Table 4 — *Distribution of patients as per various risk factors and their association with DKD*

Parameter	DKD present n=111(%)	DKD absent n=39(%)	Total N=150(%)	Chi-square	p-value <0.05 is significant
Age (years) :					
31-50	29(26.12)	21(53.85)	50(33.33)	10.326	0.0057
51-70	73(65.76)	15(38.46)	88(58.67)		
71-90	9(8)	3(7.7)	12(8)		
Gender :					
Male	48(43.24)	17(43.59)	65(43.33)	0.0014	0.97
Female	63(56.76)	22(56.41)	85(56.67)		
Blood Pressure :					
Hypertensive	81(72.97)	18(46.15)	99(66)	9.254	0.002
Normotensive	30(27.03)	21(53.85)	51(34)		
BMI(kg/m²) :					
Normal	22(19.82)	8(20.51)	30(20)	0.369	0.831
Overweight	21(18.92)	9(23.08)	30(20)		
Obese	68(61.26)	22(56.41)	90(60)		
DM duration (years) :					
0-5	24(21.62)	21(53.85)	45(30)	23.921	0.00002
6 to 10	24(21.62)	13(33.33)	37(24.67)		
11 to 15	33(29.73)	3(9.1)	36(24)		
>15	30(27.03)	2(5.1)	32(21.33)		
Retinopathy :					
Present	42(37.84)	2(5.12)	44(29.33)	14.89	0.0001
Absent	69(62.16)	37(94.87)	106(70.67)		

to have both DKD and Diabetic Retinopathy (DR) in our study. The association was found to be highly significant (p=0.0001). Even if the prevalence of retinopathy was not very high there was a high chance (95.45%) of diabetic nephropathy being present in these patients. The commonest form of retinopathy was non-proliferative present in 27(18%) patients followed by clinically significant macular edema in 9(6%) and proliferative retinopathy in 6(4%) patients.

Correlation between UACR and HbA1c, eGFR and S creatinine :

There was a positive correlation between UACR and HbA1c (R=0.184, p=0.066) levels and serum creatinine (R=0.4563, p=0.00001) according to Pearson's correlation co-efficient and a negative correlation between the UACR and eGFR (R=-0.366, p=0.00018). However, while the correlation between UACR and HbA1c was not significant, the correlation between the UACR and serum creatinine as well as eGFR was significant to a huge extent, with rising UACR, serum creatinine showed a rise and eGFR a fall in value.

Discussion

We found a 74% prevalence of diabetes as per the prevailing definition which is alarmingly high as compared to the usual figures of DKD prevalence. However, similarly high prevalence rates have been found in other studies also. In an Indian study it was found that the prevalence of DKD in Delhi was 68.4%[11,13]. Another Indian study also showed a prevalence of 68.86%[18]. There is a recent unreasonable rise in the prevalence of diabetes in India and type 2 diabetes in Asian Indians differs from their Caucasian counterparts in terms of earlier age of onset, obesity is less common and genetic predisposition, (59% patients in our study gave a positive family history of diabetes). It has been reported that Asian Indians have the highest prevalence of T2DM world over[19]. Apart from that, a high prevalence in our study might have been a result of ours being a tertiary care referral centre which caters to the lower socio-economic class. Our patients were likely to have low awareness of disease leading to longer and poor control of diabetes along-with financial restraints for follow-up and treatment of the same. Most of our patients were in KDIGO stage G2 and G3 which is in contrast to study by Farah, *et al* where 55% of patients were in stage G1 and prevalence of DKD was 50.14%[20].

In our study, we found a female predominance with 85 females in our study and a higher prevalence of DKD within females. A meta-analysis of 10 studies involving more than 5,00,000 subjects showed that the pooled adjusted risk ratio of 3.34 in women and 2.84 in men without any difference in diabetes related risk of DKD. However, it has been found that women with DKD but without End Stage Renal Disease (ESRD) have better survival than men due to a more rapid and steeper decline in the eGFR in men[21].

The mean age of patients in our study was 56.5 years and the mean duration of diabetes was 10.34 years. Considering the fact that the mean age of diabetes onset in India is 40 years[22] and the peak incidence of DKD is around after 10 to 20 years of onset of diabetes[23] after which there is a progressive decline. Our study results are consistent with this fact given the mean age, mean duration of DM and also having maximum DKD patients in the age group of 51-70 years of age. We also found a significant relationship of duration of DM with the presence of DKD both by univariate and multivariable analysis hence proving it to be a strong predictor of DKD.

The prevalence of hypertension in our study was 66% which is consistent with studies conducted by Farah, *et al*[20] where hypertension was reported in 69% patients and in 67.14% patients in a study by Bhaisare, *et al*[24] who has also quoted similar other studies having similar prevalence of hypertension. Verma, *et al* also found 66.3% of patients with DKD to have hypertension[18]. We found a significant correlation of hypertension with the prevalence of DKD in our study. Hypertension is a well-known risk factor for microalbuminuria however, we did not find any significant difference in UACR between normotensive and hypertensive patients in our study. This could be due to various other factors influencing the same like the glycemic control, duration of diabetes and age influencing UACR. However, there was a significant difference in the mean eGFR of both the groups, this was also found in the study by Verma, *et al*. Whether this difference is a cause or effect remains controversial but it does suggest that the presence of hypertension might indicate a progression of DKD and remains a strong predictor for the same.

We did not find BMI to be a predictor for DKD in our study. Although, several studies have showed BMI to be positively associated with prevalence of DKD, our study failed to do so. A study by Huang, *et al* showed that in normal weight T2DM patients, higher HOMA-IR, leptin and resistin levels were associated with higher risk of nephropathy while this was not seen with overweight and obese patients[25]. This remains an area of potential investigation in Indian patients and might be a reason for the finding in our study. Also, the use of Indian BMI classification may have

attenuated the significance of association as seen in the study by Man REK, *et al*[26].

There is a positive relation between HbA1c and diabetic nephropathy. Surprisingly, in our study we did not find this to be true. This might have been due to the reason that HbA1c though a central biomarker is not a perfect one[27]. Both, anaemia, especially iron deficiency or hemolytic as well as renal failure can lead to falsely elevated HbA1c. Also, HbA1c reflects glucose control over the preceding 3 months more so of the preceding 6 weeks and is not a predictor of very long-term glucose control[28]. It has been found that patients of DKD tend to have more incidence of anaemia as compared to their healthier counterparts[29].

We found a significant association of Diabetic Retinopathy (DR) with DKD in our study. It has been suggested that DR is a strong predictor of DKD progression and presence of severe DR increases the risk of DKD progression[30].

Limitations

The limitations of our study were a relatively small sample size from a single centre. The strengths of our study were that it was a prospective study which could generate current data. Most studies of this type are usually of a retrospective nature. We also included only those patients who had visited us for the first time so as to get a better idea about the population dynamics regarding prevalence and control of the disease.

Conclusion

In Conclusion, the prevalence of DKD is alarmingly high in type 2 DM patients and goes parallelly with the prevalence of diabetes mellitus. Duration of diabetes, hypertension and advancing age remain important risk factors for the development of DKD. Good glycaemic control remains the mainstay of prevention but HbA1c may not be a helpful biomarker for the same. The best strategy remains early detection of diabetes through screening, probably from the age of 30 onwards in our population and probably earlier with other risk factors. Prevention of diabetes remains the best intervention by following a healthy lifestyle and keeping the modifiable risk factors in check. Stringent control of hypertension remains paramount in prevention of DKD.

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