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Prevalence of Chronic Kidney Disease (CKD) in Type 2 Diabetes Mellitus Patients: START-India Study

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Abstract

Objective: Despite rising incidence of diabetes in India, we currently lack country wide data on the prevalence of CKD in T2DM patients. Hence this nationwide study was planned.

Methods: This was a nationwide, cross-sectional, observational, multi-centric study to assess prevalence of CKD among T2DM patients. The primary endpoint of the study was to estimate proportion of T2DM patients with CKD (glomerular filtration rate [GFR] <60 ml/min/1.73 m^2or albumin creatinine ratio [ACR] ≥ 30 mg/g or ≥ 3 mg/mmol or both). The blood/plasma and urine samples, were collected for estimation of hemoglobin A1c, microalbuminuria, serum creatinine, urine creatinine, and routine urine analysis.

Results: Of the 3043 screened subjects, 3000 eligible subjects were enrolled, out of which 46% were females. The mean age was 53.4 (± 11.9) years, with a mean body mass index of 27.3 (± 4.8) kg/m^2. Both micro and macro vascular complications were reported. In the studied population with T2DM, 47.8% had mildly decreased, 15.1% had mild to moderately decreased, and 1.8% had severely decreased GFR respectively. As per ACR categorization, 61.3% had normal to mildly increased ACR, 25.6% with moderately increased and 7.2% with severely increased ACR were seen. We observed a significant (p<0.0001) weak negative correlation (-0.23069) between eGFR< 60 mL/min/1.73 m^2 and urinary ACR in over six hundred patients. We found 48.4% prevalence of CKD in T2DM patients. The results on analysis of HbA1c goal achievement showed that the patients without CKD had a better success rate to achieve the target <7% goal of HbA1c compared to those who had CKD (29.6% vs. 23.4%).

Conclusion: Study reported higher prevalence of CKD which was driven by the ACR levels and majority of the patients had reasonable eGFR. This can be a guide to select drug and dosage of diabetes drug as it depends on kidney function.

Keywords: Diabetes mellitus; Diabetic nephropathy; Glomerular filtration rate (GFR); Renal insufficiency chronic

Introduction

Worldwide, diabetes mellitus (DM) has become an important public health problem, with its prevalence ranging from 6.9 to 10.2% in developed countries and almost over 7% in the developing countries [1,2]. As per the International Diabetes Federation Atlas (IDFA) for 2015, about 69 million people in India and over 415 million people across the globe are suffering from diabetes [3]. It is projected that the prevalence of diabetes will rise alarmingly, reaching up to 124 million in India, and over 640 million worldwide by 2040 [3]. Over 70% of the population with diabetes lives in low and middle income countries. Despite this high prevalence and an important public health threat, Type 2 DM (T2DM) was not recognized and not included in the United Nations millennium development goals. This rise, in prevalence of diabetes increases disease related mortality and morbidity. It also significantly enhances the burden on health care infrastructure, care givers and society [4].

The mortality and morbidity due to DM is attributed to a range of complications, which includes both micro-vascular and macro-vascular complications. One such microvascular complication is diabetic nephropathy, which is characterized by microalbuminuria, which over long period turns into macro albuminuria, causing overt nephropathy [5]. The glomerular filtration rate (GFR) also deteriorates significantly in this process. If not treated, and addressed medically, nephropathy progresses into chronic kidney disease (CKD). CKD in patients who have T2DM, is clinically defined as, elevated urinary albumin excretion ≥ 30 mg/g, a persistent reduction in the estimated GFR (eGFR) <60 ml/min/1.73 m^2, or both [6,7]. The prevalence of CKD in patients with T2DM, is estimated to be approximately 50% worldwide [8]. Also, the epidemiological changes in T2DM, are influencing or impacting the epidemiology of T2DM - associated CKD. This association of T2DM and CKD complicates the treatment of T2DM both clinically as well as financially. CKD in T2DM patients decreases the efficacy of oral anti-diabetic drugs [9]. This is indicative of the need for adjusting the dose

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of anti-diabetic drugs in T2DM patients who have CKD. CKD also significantly amplifies the risk of developing several complications if coupled with DM. These complications range from cardiovascular diseases, heart failure, renal failure, infections, adverse drug reactions to impaired quality of life and premature deaths [10-13].

Despite rising incidence of diabetes in India, we currently lack country wide robust, reliable data on the prevalence of CKD in T2DM patients. The currently available data in the public domain, is either from some specific regions in the country or it doesn't capture the prevalence of CKD specifically in T2DM population [9,14]. Therefore, it was eminent to perform a pan-India epidemiological study to get a clear cut idea on the prevalence of CKD in T2DM patients. Hence, with an objective to address this critical gap in our knowledge, which will aid in appropriate management of such patients, we performed a nationwide, cross-sectional, observational, multi-centric study to assess the prevalence of CKD among T2DM patients.

Materials and Methods

Study design and population

This study was a nationwide, cross-sectional, observational, multi-centric study to assess the prevalence of CKD among T2DM patients performed at 30 different sites (Sep. 2014 to May 2015). It was planned to enroll 3000 subjects into this study. The result of the interim analysis have been published [15]. Briefly, after approval by the local ethics committees and obtaining subjects written informed consent, adult male and female (above 18 years) Indian nationals who had T2DM were enrolled into this study. Subjects with type I diabetes mellitus, acute kidney injury, known renal transplant, history of hematuria, symptomatic urinary tract infection, and those who were on maintenance dialysis or participated in any interventional study within past 3 months, and pregnant women were excluded from the study.

Outcomes

The primary objective of the study was to estimate the prevalence of CKD in T2DM patients. The secondary objective included correlation estimation between estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 and urinary albumin creatinine ratio (ACR), estimation of proportion of T2DM patients in various categories of GFR and ACR, proportion of T2DM patients with CKD for different duration of diabetes since diagnosis, and the HbA1c goal achievement in patients with and without CKD.

Demographic and disease characteristics of subjects with data on their medical history, physical examination, vital parameters, laboratory parameters, and current medication were recorded. Medical history included both micro- and macro-vascular complications of T2DM. Laboratory investigations were done from blood/plasma and urine samples were collected from subjects and included assessment of hemoglobin A1C (HbA1C) levels, creatinine, microalbuminuria, and routine urine analysis. All of the study related information was collected at a single visit.

Subjects who had low eGFR (<60 ml/min/1.73 m^2) and/or increased ACR (≥ 30 mg/g or ≥ 3 mg/mmol) on the basis of laboratory tests performed at single visit were considered as having CKD. Stages of CKD were categorized according to the Kidney Disease Outcomes Quality Initiative (KDQOI) guidelines [16].

Calculation

- ACR was calculated from creatinine in urine and microalbuminuria result.
- GFR was calculated by Modification of Diet in Renal Disease (MDRD) equation [17]:

eGFR (mL/min/1.73 m^2)=175 × [Serum Creatinine (μmol/L)]$^{-1.154}$ × age (years)$^{-0.203}$ × 0.742 (if female).

Safety Reporting

Considering the non-interventional nature of this study, no proactive safety data collection was made. Only spontaneously mentioned safety events were reported as required by the post-marketing pharmacovigilance regulations.

Statistical Analysis

Descriptive statistical methods were used to summarize the demographic and disease characteristics. For continuous measurements such as age, the mean, median, standard deviation and range were tabulated and for the categorical measurements such as gender, the frequencies were computed. Chi-square test was performed for assessing the relationship between various anti-diabetic, anti-hypertensive and anti-dyslipidemic medications with renal failure among the study population. All statistical analyses were conducted with the SAS System, version 9.2. If a subject was confirmed to have UTI after enrollment in the study, the subject's data was excluded from the analysis. Statistical significance for correlation coefficient for association between eGFR and urinary ACR was set at $p<0.05$.

Results

Of the 3043 screened subjects, 3000 eligible subjects were enrolled into this study. There were 46% females enrolled into this study. The mean age of the subjects were 53.4 (± 11.9) years, with a mean body mass index of 27.3 (± 4.8) kg/m^2. The systolic and diastolic blood pressure and hematological and general chemistry parameters like HbA1c, serum creatinine, albumin, creatinine and eGFR are listed in Table 1. Subjects reported both micro and macro vascular complications with neuropathy to be highest 13.7%, nephropathy in 4.17%, and 6.1% had known coronary artery disease. The details of the duration of these co-

Baseline Characteristics	T2 Diabetes Mellitus Patients (n=3000) Mean (± SD)
Age (years)	53.4 (11.86)
Gender n (%)	
Female	1382 (46.1%)
Male	1618 (53.9%)
	161.0 (9.75)
Height (cm)	
Weight (Kg)	70.9 (13.57)
Waist (cm)	97.0 (11.56)*
BMI (Kg/m^2)	27.3 (4.75)
Blood pressure (mmHg)	
Systolic	132.4 (16.07)
Diastolic	79.5 (8.99)
Pulse rate (beats/min.)	80.7 (9.39)
Hematology and general chemistry	
HbA1c (n=2992)	8.4 (1.94)
Serum Creatinine/dL (n=2994)	1.0 (0.79)
Albumin (mg/L) (n=2841)	133.7(844.64)
Creatinine (mg/dL) (n=2981)	96.0 (72.62)
eGFR*** (ml/min/1.73 m2) (n=2994)	77.3 (26.56)

Table 1: Baseline characteristics, *Excluded the patients from the analysis.

morbid conditions are listed in (Table 2). In the studied population with T2DM, had mildly decreased (47.8%), 15.1% had mild to moderately decreased, and 1.8% had severely decreased GFR respectively.

One of the secondary objectives was to ascertain the stages of CKD on the basis of eGFR and ACR. As per ACR categorization, 61.3% had normal to mildly increased, 25.6% with moderately increased and 7.2% with severely increased ACR respectively, as shown in (Table 3). We have observed a significant ($p<0.0001$) weak negative correlation (-0.23069) between eGFR< 60 mL/min/1.73 m^2 and urinary ACR in over six hundred patients.

We have found 48.4% prevalence of CKD in T2DM patients. The results on analysis of HbA1c goal achievement showed that the patients without CKD had a better success rate to achieve the target <7% goal of HbA1c compared to those who had CKD (29.6 vs. 23.4%), details are listed in Table 4. We have also investigated the similar proportion of subjects with a history of diabetes, which ranged from less than 5 to 10+ years.

Discussion

The present study aimed at assessing the prevalence of CKD in T2DM subject's across the country. CKD in T2DM patients is characterized by a persistent elevated urinary albumin creatinine ratio (ACR) ≥ 30 mg/g, a persistent reduction in estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2, or both. Worldwide several large cross sectional studies have been carried out to assess the CKD prevalence and they have reported a prevalence of around 50% of patients with T2DM [18]. We proposed a combined use of eGFR and ACR for early detection of renal dysfunction as against serum creatinine, a common measurement for kidney function in routine practice, considering it to be a poor marker of kidney dysfunction [19]. We adopted MDRD equation to compute eGFR. Another, important marker for kidney impairment is albuminuria, Albumin Creatinine Ratio (ACR). Also, there are reports on the significant correlation between ACR and eGFR. With these changes in the study design and estimation parameters we attempted to get the best possible estimation of the CKD prevalence.

We reported a 48.4% prevalence of CKD in T2DM patients in across the population enrolled at several centers in India which is in line with the other reported numbers. A similar study from US with a sample size comparable to ours, presented a similar CKD prevalence of 43.5% (95% confidence interval: 41.6-45.4) [20]. In PERCEDIME2 study from Spain, the prevalence of CKD was estimated to be 27.9% in 1145 T2DM patients of >40 years of age [21]. Similarly in another study conducted in Thailand, prevalence of CKD stage 3-5 were 27.09 and 25.28% [22]. In another Spanish study, the prevalence of CKD in T2DM patients treated at primary care level was 34.6% [23]. Further, study done by Janmohamed et al. found CKD in 83.7 % of diabetics which is relatively higher than the prevalence reported elsewhere [24]. In Singapore, a study performed at a primary care cluster, consisting of multi-ethnic

Medical History	n (%)	Duration in months
		Mean (± SD)
Duration of Type II Diabetes Mellitus		97.5 (84.83)
Dyslipidemia	1283 (42.8)	-
Hypertension	1613 (53.8)	-
Micro vascular Complications	572 (19.1)	
Retinopathy	127 (4.23)	28.1 (29.86)
Neuropathy	411 (13.7)	29.2 (33.45)*
Nephropathy	125 (4.17)	38.7 (48.97)
Other	34 (1.13)	35.4 (41.73)
Macro vascular Complications	215 (7.17)	
Known CAD**	182 (6.07)	50.6 (43.77)
Stroke	29 (0.97)	50.0 (53.45)
Peripheral arterial disease	13 (0.43)	47.8 (47.77)*
Other	04 (0.13)	52.3 (43.45)
*Information for one patient was missing, ** CAD; coronary artery disease.		

Table 2: Medical history of enrolled patients.

Categories	Patients
GFR categories in CKD	(n=3000) n (%)
GFR categories in CKD	
G1 (Normal or High)	843 (28.1)
G2 (Mildly decreased)	1433 (47.8)
G3a (Mild to moderately decreased)	453 (15.1)
G3b (moderately to severely decreased)	188 (6.3)
G4 (Severely decreased)	55 (1.8)
G5 (Kidney Failure)	22 (0.7)
Missing	6 (0.2)
As per urinary ACR* categories in CKD	
A1 (Normal to mildly increased)	1840 (61.3)
A2 (Moderately increased)	767 (25.6)
A3 (Severely increased)	215 (7.2)
Missing	178 (5.9)
Correlation between eGFR <60 ml/min/1.73m2 and urinary ACR	(N=672#)
Correlation Coefficient	-0.23069
p-value	<0.0001
ACR=Albumin to Creatinine Ratio, CKD=Chronic Kidney Disease, GFR values (ml/min/1.73 m^2): G1=>=90, G2=60-89, G3a=45-59, G3b=30-44, G4=15-29, G5=<15 ACR (mg/g): A1=<30, A2=30-300, A3=>300 *Excluded the patients from the analysis if i. Patients whose urinary ACR and eGFR values are missing ii. Patients whose urinary ACR value <30 mg/gm and eGFR is missing iii. Patients whose urinary ACR value is missing and eGFR>=60 ml/min/1.73 m^2 # Patients with missing value of eGFR or urinary ACR were excluded from the analysis. 5% level of significance used for the analysis.	

Table 3: Details of CKD Stages among type 2 diabetes mellitus patients.

Characteristics	Patients
	n=2866* (%)
T2DM patients without CKD	1478 (51.6)
HbA1C <7.0 %	437 (29.6)
T2DM patients with CKD	1388 (48.4)
HbA1C <7.0 %	324 (23.4)
Duration of Type 2 Diabetes Mellitus	
0 years	3 (0.22)
<5 years	466 (33.6)
5 to 10 years	454 (32.7)
>10 years	465 (33.5)
HbA1c; Glycated Hemoglobin, CKD=Chronic Kidney Disease, Excluded the patients from the analysis if, i. patients whose urinary ACR and eGFR values were missing, ii. patients whose urinary ACR value <30 mg/g and eGFR was missing, iii. patients whose urinary ACR value was missing and eGFR >=60 ml/min/1.73 m^2	

Table 4: Summary of HbA1c goal achieved and duration of Type 2 diabetes mellitus.

Asian population, prevalence of CKD in T2DM patients found to be 53% [25].

We classified the CKD stages based on the KDIGO guidelines and found that around 47.8% patients had mildly decreased, 28.1% had normal to high, and 15% patients of our study had mild to moderately decreased eGFR value respectively. An interesting study by Rajapurkar et al. [25] in a first report of the Indian CKD registry, inferred that diabetic nephropathy was commonest cause (31%), followed by CKD of unknown etiology (16%). They also reported that around 48% cases were in stage V and these patients were younger than those in Stages III-IV. The patients with diabetic nephropathy were older, presented earlier stages of CKD and more often males. Our results are in line with these reported by Rajapurkar et al. [26]. A similar study conducted in US, reported prevalence of CKD based on either eGFR or UAE to be 43.5% in the T2DM population overall, and 61.0% in those aged ≥ 65 years. They reported a prevalence of mildly decreased renal function or worse (eGFR <60/ml/min/1.73 m^2) to be 22.0% overall and 43.1% in those aged ≥ 65 years. Severe renal impairment was reported to be 9.0% in entire cohort and 18.6% in the older population. This higher prevalence of G4 stage can be attributed to about 50% patients who were >60 years of age in US study. In our study we found only 1% patients with kidney failure (GFR <15ml/min/1.73 m^2 and severe renal impairment (GFR 15-40 ml/min/1.73 m^2) in 1.8% of T2DM patients. Our study revealed that about 25% of the patients had microalbuminuria (stage A2), while macroalbuminuria (A3) was present in 2.0% patients. Microalbuminuria is a known indicator of renal dysfunction and also prognosticator of cardiovascular disease [27]. Thus, our results represented the proportion of T2DM patients in Indian population with different stages of CKD based on eGFR and albuminuria.

We investigated the duration of T2DM in patients with CKD. The proportion of T2DM patients with CKD were almost equal (approximately 30%) for different durations of T2DM since diagnosis (<5years, 5-10 years, and >10 years). A similar study from Bangladesh also found no significant correlation between duration of T2DM (< 5 years or 5-10 years) and renal function parameters (serum creatinine, ACR, eGFR,) [28]. However, a Chinese study revealed significant association of CKD with duration of diabetes [29].

An interesting observation from our study, we observed that possibility of CKD prevalence in T2DM patients is independent of duration of diabetes post diagnosis. Hence, it is recommended to screen for CKD in T2DM patients, soon after diagnosis of diabetes because usually there is delay in diagnosis after onset of T2DM [30].

We analysed HbA1c goal attainment of <7% in T2DM patients with/without CKD. The result of our study suggested that lesser proportion of patients with CKD (23.4%) had achieved the target HbA1c level as compared to those without CKD (30%). Onset of CKD can be prevented/delayed at early stages by optimal glycaemic control [30]. As per KDOQI clinical practice guidelines, diabetic patients should have target of <7.0% for HbA1C regardless of the presence or absence of CKD [31]. But, target of 7% to 8% is acceptable for patients with severe comorbidities like CKD [32]. A recent study from Italy reported, despite using anti-diabetic drugs in T2DM patients, CKD was associated with failure in achievement of recommended target for HbA1C [33].

In order to improve the glycaemic control of T2DM patient with renal complication, there is a need to identify the factors linked with glycaemic control [34]. Our result also indicated that poor control of HbA1c is an indicator of renal insufficiency and that there is need for investigating concomitant renal disease in patients with T2DM. Haque N et al, found correlation of HbA1c with serum creatinine and ACR and concluded that in monitoring diabetes mellitus, poor control of HbA1c is suggestive of need for renal function tests [28]. We support this approach as our findings reflect that less proportion of T2DM patients with CKD achieved HbA1C goal.

Our study was not devoid of the limitation of any cross sectional study, this was a single time one visit assessment, and the sample size was not too large to extrapolate these findings to the general population.The detection of the presence of kidney disease based on eGFR and albuminuria was made solely on a single random sample of the laboratory values, so we could not estimate the chronicity of the observations. Due to the cross-sectional nature of this pan India study, we failed to ascertain the outcomes such as CKD progression and mortality.

In conclusion, this study reported a high prevalence of CKD in T2DM patients in India. This high prevalence was driven by high proteinuria but reasonable eGFR. This insights will be a good guide to select diabetes drug as choice of many class of drugs depends on kidney function.

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