

# Role of GFR Estimation in Assessment of the Status of Nephropathy in Type 2 Diabetes Mellitus

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## Abstract

**Objectives :** Study the status of glomerular filtration rate (GFR) estimation vis-à-vis other noninvasive modes of assessment of renal involvement in Type2 Diabetes Mellitus (T2DM) and assess the temporal profile of the prevalence of nephropathy with a cross sectional cohort.

**Methods :** A total of 100 patients of T2DM were selected after screening and segregated into 3 groups according to duration of T2DM. Duration of < 5 years constituted group A and had 31 patients, group B duration was between 5-15 years and had 40 patients, rest belonged to group C with duration > 15 years. The parameters studied and compared were (1) various grades of albuminuria - normal, micro and macro by 24 hrs. urinary albumin excretion rates (UAER- gm/24 hr), (2) sonologically detected renal size(normal, small, large) and morphology (loss or presence of corticomedullary differentiation, (3) serum creatinine level (</> 1.4 mg/dl) and (4) different levels (high, normal, low, very low) of GFR (ml/min) by DTPA renal scan.

**Result Analysis :** There was high prevalence of nephropathy in all durations. Microalbuminuria had a high prevalence in patients of shorter duration (group A-74.2%). Albuminuria increased with duration but plateaued off with longer duration (> 15 yrs) (UAER -  $0.0842 \pm 0.083$  vs.  $0.906 \pm 0.84$  vs.  $1.346 \pm 1.28$ ). Sonographic loss of corticomedullary differentiation and azotemia were late feature only and none had a contracted kidney. Only the parameter of GFR showed a graded and rather linear decrement with duration ( $132.57 \pm 19.3$  vs.  $76.33 \pm 20.8$  vs.  $40.08 \pm 17.1$ ). Hyperfiltration had a high prevalence in patients of early detection (61.3%) and was the earliest change noted before change in any other parameter. GFR shows wide variation in various grades of albuminuria, especially microalbuminuria, and azotemia. A value in the normal range was uncommon (8%).

**Conclusion :** GFR estimation is probably the most rational noninvasive mode of assessing the renal status in patients of T2DM, irrespective of the status of the other noninvasive methods as they express significant variation in inception and progression. ©

## INTRODUCTION

Diabetic nephropathy as a complication of type 2 Diabetes Mellitus (T2DM) poses a serious problem in terms of financial load, morbidity and mortality in the developed world.<sup>1</sup> The natural history is characterized by a progressive rise in urinary albumin excretion from normo albuminuria to clinical proteinuria, relentless declining of glomerular filtration rate (GFR), rising blood pressure, ultimately culminating in end stage renal disease (ESRD).<sup>2,1</sup> In non-Caucasian diabetic patients especially Indo-Asians microalbuminuria is commoner as is progression to ESRD.<sup>3</sup> Factors associated with progression include

glycemic control, baseline albumin excretion, hypertension, dyslipidaemia, age, sex, and duration of diabetes mellitus (DM), ethnicity and smoking status.<sup>4,6</sup> With equal control of mean blood pressure subjects of African descent are at a seven-fold increased risk of progression to ESRD compared to whites.<sup>3</sup> Reduced nephron endowments (fetal growth retardation) as well as reduced renoprotective effect of ACE inhibition and genetic susceptibility are important factors in Asians.<sup>5,6</sup> Many T2DM patients do not progress to ESRD but die prematurely of cardiovascular disorders.<sup>4,20</sup> Screening for microalbuminuria in T2DM has been considered controversial, though most authorities now recommend it.<sup>4</sup> Studies in the Indian perspective show a relatively low prevalence of nephropathy in T2DM.<sup>7-9</sup> However, delineation of the renal status with duration of diabetes by measuring glomerular filtration rates (GFR) is lacking.<sup>10,11,7</sup>

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**Table 1 : Total no. of patients = 100(= %)**

Paramet.→ Group	UAER (gm/24 hr)			USG			Total GFR(ml/min)				SR. CR. (mg/dl)	
	<0.03	0.03-0.299	≥0.3	N	LND	LLD	<30	30-110	N 110-120	>120	≤1.4	>1.4
A n=31	8 (25.8)	23 (74.2)	0	5 (16.1)	26 (83.9)	0	0	4 (12.9)	8 (25.8)	19 (61.3)	30 (96.8)	1 (3.2)
B n=40	0	8 (20)	32 (80)	0	32 (80)	8 (20)	0	38 (95)	0	2 (5)	40 (100)	0
C n=29	0	9 (31)	20 (69)	0	7 (24.1)	22 (75.9)	11 (37.9)	18 (62.1)	0	0	16 (55.2)	13 (44.8)

## AIMS AND OBJECTIVES

To study the renal abnormalities in T-2 DM patients, find its pattern of progression over time with the help of matched populations of a cross-sectional cohort by the estimation of GFR, and assess its status vis-a-vis other commonly used noninvasive measures like degree of albuminuria, ultrasonography of the kidneys and serum creatinine level.

## RESEARCH DESIGN

Consecutive patients of T-2 DM were collected, screened, matched and investigated from the Diabetes Clinic of N.R.S. Medical College, Kolkata from January 2001 to December 2002. They were divided into 3 sub-groups depending on the duration of initial detection of T2DM. Group A constituted patients with < 5 years duration, group B 5-15 years and group C > 15 years duration. The duration selection of the groups was partly arbitrary and partly according to the internationally accepted progression profiles in cases of type-I DM.<sup>4,6</sup> Thorough clinical examination was performed. Groups were matched by BMI (body mass index), sex ratio, systolic and diastolic blood pressure (when the patient first presented to the research group), total cholesterol level, triglyceride level, HbA1C% and smoking status (however, they were not matched by cumulative mean plasma glucose and blood pressure, HDL and LDL levels)<sup>12,5,1</sup> Patients with nonsterile urine, presence of heavy hematuria, ketone bodies, rapid deterioration of renal function and or acute nephritic syndrome, active inflammation or infection elsewhere, pregnancy, congestive cardiac failure and recently detected T-2 DM with nephrotic range proteinuria were excluded.<sup>13,3,7</sup>

Twenty four hour urinary albumin excretion rate (UAER), estimated by immunoturbidimetric method, and serum creatinine levels (autoanalyser) were assessed on 3 occasions 0 to 4 months apart under similar clinical conditions without any water loading or diuretic therapy and the average was taken.<sup>14,6,1</sup> Ultrasonography (USG) for renal size (contracted, normal, enlarged) and noninvasive morphology (corticomedullary differentiation present or lost) was done twice at 1-2 months interval.<sup>15</sup> DTPA renal scan for estimation of total (sum of both kidneys) glomerular filtration rate (GFR) was performed once in each patient.<sup>14</sup> Prior to the

**Table 2 : Total no. of patients = 100**

Group	UAER gm/24 hr	GFR ml/min	SR. CR. mg/dl
A n=31	0.0842 ± 0.083	132.57 ± 19.3	0.965 ± 0.24
B n=40	0.906 ± 0.84	76.33 ± 20.8	1.06 ± 0.16
C n=29	1.346 ± 1.28	40.08 ± 17.1	2.52 ± 2.06

Abbreviations used in Table 1 and Table 2 :

Paramet.-parameters of renal functions, UAER – urinary albumin excretion rate, USG – ultrasonography, N – normal, LND – large kidney with normal corticomedullary differentiation, LLD – large kidney with lost corticomedullary differentiation, GFR – glomerular filtration rate, SR. CR. – serum creatinine, n = number of patients

investigations (UAER, serum creatinine, USG, DTPA) all patients were made normoglycemic and normotensive for at least 2 weeks.<sup>14,15</sup> UAER of < 30mg/24 hr was taken to be normoalbuminuria, between 30 and 299 it was microalbuminuria and > 300 mg/24 hr was considered clinical proteinuria or macroalbuminuria.<sup>14,5</sup> A GFR of < 30 ml/min was considered very low, between 30 and 110 was leveled as low, normal was between 110 and 120 (a group of 14 non-diabetic, non-hypertensive persons of similar mean age and BMI were studied as controls for estimating normal GFR which ranged between 108.6 to 123.2) and above 120 ml/min. was defined as hyperfiltration.<sup>16,17</sup> A fasting serum creatinine value of > 1.4 mg/dl was considered to be raised creatinine.<sup>14</sup> Statistical analysis was done by standard error of two means and two proportions for a large sample. A 'p' value of < 0.05 was taken to be of significance.

## OBSERVATIONS

A total of 252 patients were screened, of which 113 were excluded for the purpose of matching. 39 patients could not complete all the investigations and or was lost in follow-up. Ultimately the study was done with 100 patients of whom 31 belonged to group A, 40 to group B and 29 in group C. Table 1 depicts the distribution of various levels of albuminuria, USG profiles, GFR break ups and serum creatinine levels within the three groups. Table 2 enumerates the distribution of the values of albumin excretion rate, total GFR and serum creatinine as mean ± standard deviation

amongst the three groups.

The overall prevalence of all forms of renal affections together exceeds 90%. A total of 14 patients (14%) who had sr. creatinine value > 1.4 revealed a mean GFR of  $29.8 \pm 18.5$  ml/min, 30 patients (30%) had loss of corticomedullary differentiation on USG and showed a mean GFR of  $38.9 \pm 14.6$  ml/min. In group A, eight patients (25.8%) had normoalbuminuria and expressed a mean GFR of  $131.3 \pm 17.1$  ml/min, 19 patients (61.3%) showing GFR > 120 (hyperfiltration) had mean UAER of  $0.059 \pm 0.02$  gm/24 hr. Normoalbuminuria and microalbuminuria were significantly higher in group A (25.8% and 74.2%). Macroalbuminuria was higher in both group B and C (80% and 69%). Most of the patients of group A and B had a large kidney with preserved corticomedullary (CM) differentiation (83.9% and 80%); only group C had a significantly higher prevalence of large kidney with loss of CM differentiation (75.9%). Group A showed a significantly higher prevalence of normal and raised GFR (25.8 % and 61.3%). Group B had a significantly higher prevalence of low GFR, while prevalence of very low GFR was highest in group C (37.9%). High level of serum creatinine was only significantly associated with group C (44.8%).

For UAER group A had a significantly lower level compared to both B and C ( $p < 0.01$ ), however, there was no significant difference between group B and C with respect to the amount of both micro and macro albuminuria. The GFR had a progressively significant decrement from group A through Group B to C ( $p < 0.01$ ). There was no difference between group A and B as far as the serum creatinine was concerned, however, there was significant difference ( $p < 0.01$ ) with group C. Patients with raised creatinine and loss of CM differentiation on USG showed the lowest GFR, but the difference ( $29.8 \pm 18.5$  vs.  $38.9 \pm 14.6$ ) was not statistically significant. Only one patient of group C had a GFR < 10 ml/min.

## DISCUSSION

Cross-sectional studies have shown that the prevalence of microalbuminuria ranged between 10% and 42%;<sup>18,19,2,8</sup> with a high prevalence of large bright kidney.<sup>16</sup> The prevalence of renal involvement in T2DM was found to be very high in our study compared to the other Indian studies.<sup>6,7</sup> Microalbuminuria had a very high prevalence (74.2%) in patients of early diagnosis too. These are probably reflections of a high prevalence of the insulin resistant state in our population as other commonly associated renal disorders in this age group have been meticulously searched for and excluded.<sup>13,19</sup> Macroalbuminuria increases with duration of more than 5 years, but it does not increase significantly beyond 15 years which is probably associated with loss of nephron number and progressive fall in GFR.<sup>3,18</sup> The relation of prevalence of microalbuminuria to duration of T2DM is

apparently not as strong as in type-1 DM.<sup>1,3</sup>

Rise of creatinine, with or without loss of CM differentiation, was a rather late manifestation. Renal ultrasound examination is helpful if the renal size is normal or increased and kidneys are symmetrical, as diabetic glomerulosclerosis is likely.<sup>2,10</sup> Enlarged kidney had a very high incidence in all the subgroups (83.9% - 100%) with loss of CM differentiation being significantly associated with only group C; however, there was no patient with a small kidney size. Probably, both serum creatinine and renal volume has to be indexed with lean body mass and or body surface area before they become rational early markers.<sup>14,16</sup>

Fall of GFR was relentless though albuminuria stabilizes or even decreases with longer duration. A very low GFR was significantly associated with a raised creatinine level and loss of CM differentiation in USG. All patients of normoalbuminuria showed raised GFR, and 50% of the patients with raised GFR had early microalbuminuria but none had macroalbuminuria. GFR remains high and or normal with the onset of microalbuminuria only beginning to decline with development of late micro or early macroalbuminuria without azotemia.<sup>12,1</sup>

End stage renal disease as a percentage is still very low, the cause of which is probably increased cardiovascular mortality and not a better management strategy as the prevalence of albuminuria (micro and macro) is still very high in our population.<sup>20</sup> We can expect a higher percentage of ESRD in the coming decade if cardiovascular mortality improves.<sup>5</sup>

## CONCLUSION

Grades of albuminuria express a variable progression over time and it plateaus off with longer duration.<sup>1,18</sup> Contracted renal size might be helpful in excluding diabetic renal disease.<sup>9</sup> Azotemia is a late finding only. Only the parameter of GFR exhibits a full spectrum of changes ranging from hyperfiltration at a stage when changes in the other parameters are not at all apparent; and then a progressive decrement with increasing duration in a near linear fashion.<sup>1,3</sup> So, GFR estimation is the only renal parameter which can singly provide a picture of the actual renal status of T2DM patients at any duration irrespective of the status of albuminuria, azotemia or renal size and morphology as their variability or progression is non-linear.

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For further enquiry, Kindly contact : **Dr. Rakesh Gupta**, Organising Secretary Cum Course Director, Echo and Color Doppler Centre, Sunder Lal Jain Hospital, Ashok Vihar - III, Delhi 110052.

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