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General Medicine

ANALYSIS OF GLOMERULAR FILTERATION RATE IN NON-ALBUMINURIC TYPE-1 AND TYPE-2 DIABETES MELLITUS IN EARLY DETECTION OF CHRONIC KIDNEY DISEASE

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ABSTRACT **AIMS & OBJECTIVES:** To Analyse Glomerular Filteration Rate in Non Albuminuric type 1 and type 2 Diabetes Mellitus patients, defined as glomerular filteration rate less than 90 ml/min per 1.73 m² body surface area for early detection of chronic kidney disease.
METHODS: All type 1 and type 2 diabetes mellitus patients in out patients and inpatients admitted in Department of General Medicine, Osmania General Hospital, Hyderabad.
RESULTS: Out of 186 patients 161 were categorized to Type2 DM and 25 to Type 1 DM. Among males 14(13%) were type 1 DM and 97 (87%) were type 2 DM. 11 (14%) females fell under the category of type 1 DM and 64 (86%) in type 2 DM.

KEYWORDS : Type 1 & 2 Diabetes, Glomerular Filteration Rate, Non-Albuminuric, Chronic Kidney Disease

INTRODUCTION

Diabetes is a metabolic disorder of multiple causes characterized by chronic hyperglycemia and disorders of carbohydrate, fat and protein metabolism. It results from defects in insulin secretion (type 1), insulin action (type 2) or combination of these factors1. Diabetes has become the most common single cause of end-stage renal disease (ESRD) in India and worldwide[1].

The World Health Organization estimated that there were 135 million diabetics in 1995 and this number would increase to 300 million by the year 2025. In the 1970s, the prevalence of diabetes among urban Indians was reported to be 2.1 per cent and this has now risen to 12.1 per cent[2].

India leads the world with largest number of diabetic subjects earning the dubious distinction of being termed the "Diabetes capital of the world". According to the Diabetes Atlas 2006 published by the International Diabetes Federation, the number of people with diabetes in India currently around 40.9 million is expected to rise to 69.9 million by 2025.[3]

Diabetic nephropathy is one of the leading causes of chronic renal failure in India. Among 4837 patients with chronic renal failure seen over a period of 10 years, the prevalence of diabetic nephropathy was 30.3% followed by chronic interstitial nephritis (23%) and chronic glomerulonephritis (17.7%). A study had indicated that the risk of CVD was 3-fold higher in nephropathy group than in the non-proteinuric subjects.

Prevalence of diabetes was found to be lower in the low socio-economic group living in urban areas compared with the high-income group (12.6 vs 24.6% in subject's years)[4]

MATERIALS AND METHODS

Random plasma glucose concentration > 200 mg/dl, Fasting plasma glucose > 126 mg/dl, 2 hr plasma glucose > 200 mg/dl during a 75 g OGTT. For asymptomatic individuals with any one of the above values, a 75 g OGTT is required to confirm the diagnosis.

The GFR per 1.73 m² BSA was calculated with serum creatinine, urea nitrogen, and albumin levels using an equation developed from the Modification of Diet in Renal Disease (MDRD) Study, as follows:
$$GFR = 170 \times [\text{serum creatinine}]^{-0.999} \times [\text{age}]^{-0.176} \times [0.762 \text{ if female}] \times [1.180 \text{ if non-Hispanic black}] \times [\text{blood urea nitrogen}]^{-0.170} \times [\text{serum albumin}]^{-0.318}$$

INCLUSION CRITERIA

1. 40 years of age or older and completed a standardized interview and a detailed physical examination and classified as having type 2 DM according to the American Diabetes Association (ADA)
2. Type 1 DM with a duration of at least 10 years
3. Normoalbuminuric
4. serum creatinine <2.0 mg/dl

EXCLUSION CRITERIA

Patients known to be microalbuminuric before antihypertensive therapy was started were not eligible for this study and those who were on ACEI / ARBS were excluded.

Out of 406 diabetic individuals evaluated during the study period 73 were excluded due to elevated sr. creatinine, 75 had macro proteinuria, 57 was diagnosed to have micro albuminuria and 25 were eliminated since they were on ACEI / ARBS. Leaving 186 patients for study.

RESULTS

Out of 186 patients 161 were categorized to Type2 DM and 25 to Type 1 DM. Among males 14(13%) were type 1 DM and 97 (87%) were type 2 DM. 11 (14%) females fell under the category of type 1 DM and 64 (86%) in type 2 DM

TABLE 1: TYPE OF DIABETES MELLITUS AND SEX DISTRIBUTION

S. NO	TYPE OF DM	MALE		FEMALE	
		NO.	%	NO.	%
1.	TYPE 1	14	12.61	11	14.67
2.	TYPE 2	97	87.39	64	85.33
	TOTAL	111	100	75	100

Among Type 1 DM,16 (64%) patients had duration of diabetes for 11 - 15 years with mean duration of illness 15(± 6)years with maximum of 35 years. In type 2 DM 66(41.2 %) patients were recently diagnosed with mean duration of 5 (± 6) years and maximum of 34 years.

TABLE 2. RELATION OF TYPE OF DIABETES, SEX, RETINOPATHY TO GFR

		TYPE 1 DM RETINOPATHY IN RELATION TO GFR			TYPE 2 DM RETINOPATHY IN RELATION TO GFR		
		>90	60-89	30-59	>90	60-89	30-59
MALE	BR	0	0	2	0	2	18
	PR	0	0	4	0	1	13
FEMALE	BR	0	0	0	0	1	6
	PR	0	0	0	1	1	2

BR-BACK GROUND RETINOPATHY
PR- PROLIFERATIVE RETINOPATHY

39 patients with type2 DM had retinopathy whose GFR were less than 60ml/min while only 6 patients with type 1 DM patients with retinopathy had GFR < 60 ml/min.

TABLE 3: GFR OF STUDY GROUP WITH REFERENCE TO STAGES OF CHRONIC KIDNEY DISEASE

S.NO	GFR ml/min	TYPE 1 DM				TYPE 2 DM			
		NO.	%	NO.	%				
		M	F	M	F	M	F	M	F
1.	> 90	5	5	20	20	20	8	12.4	4.9
2.	60—89	2	1	8	4	19	18	11.8	11.1
3.	30--59	7	5	28	20	58	38	36	23.6
4.	15--29	--	--	--	—	—	—	—	—
5.	< 15	—	—	—	—	—	—	—	—

Glomerular Filteration Rate, Modification of Diet in Renal Disease, in our study under type 1 DM category 12% under stage 2 CKD comprised 8 % of males and 4% of females. Out of 48% under stage 3 of CKD 28% were males and 20% were females respectively in absence of microalbuminuria.

Similarly under type 2 DM category 22.9% under stage 2 CKD comprised 11.8 % of males and 11.1% of females. Out of 59.6% under stage 3 of CKD 36% were males and 23.6% were females respectively in absence of microalbuminuria.

DISCUSSION

Long-standing type 1 diabetic patients with normal albumin excretion rate are still at risk of developing clinically significant nephropathy.

In the present study out of 406 patients which included both type1 DM and type 2 DM 18% had macro-albuminuria and 14% had microalbuminuria and 45% had normal albuminuria.

In the present study 23% were recently diagnosed and 20% and 10% with the duration of illness for 6-10 years and 11-15 years in type 2 DM category. Only 64.2% (n=45) of type 2 DM were on regular treatment. All type 1 DM were on regular insulin treatment. Albuminuria (spot urine albumin/creatinine ratio) were absent in 30% of elderly type 2 diabetic patients with GFR <60 ml/min per 1.73 m^2 (Modification of Diet in Renal Disease [MDRD] formula). Adults with type 2 DM and CKD were more likely to have macroalbuminuria (19%), microalbuminuria (45%), and diabetic retinopathy (28%).

Caroline K. Kramer and colleagues in their study reported out of total 660 normoalbuminuric type 2 diabetic patients were evaluated, Eighty-four (12.7%) had low GFR (15-60 ml/min per 1.73 m^2), and the remaining 576 comprised the reference group (87.2%). The group of patients with low GFR was older (62.9 ± 10.3 vs. 56.8 ± 9.5 years), had more women (77.4 vs. 60.2%)[5].

The prevalence of micro- and macrovascular diabetes complications in low GFR group was-diabetic retinopathy: 28.4% $P = 0.037$; coronary heart disease: 29.2% $P = 0.729$; peripheral vascular disease: 33.3 %, $P = 0.089$; and cerebrovascular disease: 7.7%. $P = 0.218$[6].

In the present study out of 186 patients which included both type1 DM and type 2 DM,18% had macro-albuminuria and 14% had microalbuminuria and 45% had normo albuminuria. Males were predominantly affected than females. Older individuals were commonly affected as seen in Richard J. MacIsaac and colleagues study[7].

Vincent Rigalleau et al in their study of 89 patients with diabetes and a modification of diet in renal disease (MDRD) estimated GFR (e-GFR) <60 ml/min per 1.73 m^2 underwent a 51Cr-EDTA B-isotopic GFR determination and were followed up for 38 ± 11 months.

The mean MDRD e-GFR (41.3 ± 13.1 ml/min per 1.73 m^2) did not significantly differ from thei-GFR (45.6 ± 29.7). Of the subjects, 15 (17%) were normoalbuminuric. Their i- GFR did not differ from the albuminuric rate and from their MDRD e-GFR, although their serum creatinine was lower (122 ± 27 vs. 160 ± 71 pmol/l, $P < 0.05$): 71% would not have been detected by measuring serum creatinine (sCr) alone. They were less affected by diabetic retinopathy. (P<0.05 Vs. albuminuric)[8].

Microalbuminuric and macroalbuminuric patient biopsies were mainly classified as Class II. Therefore, typical renal structure changes of DN were observed in T2DM patients with elevated levels of albuminuria, whereas in normoalbuminuric renal insufficiency these changes were less frequently seen[9].

The existence of this new prevalent non-proteinuric phenotype in DN raises the question if albumin is indeed the best clinical predictor marker and screening test for CKD in diabetic patients[10].

Many studies have been conducted with the aim of finding new markers to replace or at least combine with albuminuria. Some investigated the concentration of inflammatory markers of TNF pathway (free TNFα, Total TNFα, TNFR1, TNFR2) and concluded that the risk for ESRD in T2DM was strongly associated with higher concentrations of circulating TNFR1 and TNFR2[11].

L-FABP significantly correlated with the albumin levels in all patients, it did not correlate with urinary albumin levels in the subgroup with GFR above 60 mL/min per 1.73 m^2.[12].

Another possibility is that the so called non-proteinuric phenotype is actually caused by non-diabetic renal disease(NDRD), that causes GFR decline. The Soleymanian et al study, evaluated 46 T2DM patients. 34.8% had DN and 43.5% NDRD and 21.7% NDRD superimposed with DN.[13].

CONCLUSION

- In conclusion, more than 50% adults 40 years of age or older with type 2 Non albuminuria DM and patient with type 1 non albuminuria DM for more than period of 10 years had CKD either in stage 1 or stage 2.
- 36%(n=9/25) of males and 24%(n=6/25) of females had low GFR (GFR=< 90 ml/min) under type 1 DM. Similarly, in type 2 DM (n=77/161) 47.8% males and (n=56/161) 34.7% females had decreased GFR in absence of albuminuria.
- 25% with CKD were less than 50years and 55.3% were more than 50years old and 16% of females and 8% males with retinopathy had low GFR in type 1 DM group. While 16.7% males and 11.1% females with retinopathy had low GFR in type 2 DM group.

(I) The results suggest that serum creatinine levels should be measured and GFR to be estimated in all diabetic individuals who are at risk of developing nephropathy in addition to monitoring urine albumin excretion and funduscopic changes to screen for kidney disease.

(ii) Because it would not be practical to perform renal biopsies in all normoalbuminuric patients, it is recommended that long-standing normoalbuminuric diabetic patients with retinopathy or hypertension should have GFR measured on a regular basis.

(iii) Since the night time ambulatory blood pressure values and "nondipper" status were significant predictors of progression from normoalbuminuria to microalbuminuria in diabetic patients night time monitoring of blood pressure should be done in those who are at risk of developing diabetic nephropathy

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