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Original Research Article

Microalbuminuria: An Early Indicator of Kidney Dysfunction in Type 2 Diabetes Mellitus in Tribal Population of Bankura, West Bengal, India

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ABSTRACT

Diabetes mellitus (DM) is an age-old disease affecting all the organs in the body. More than 90% of DM belongs to type 2 (T2DM). Deterioration of kidney function was noted among diabetic patients in different studies. Microalbuminuria is the earliest reversible change that can be observed in prolonged history of uncontrolled DM. Present study was conducted among the non-addicted tribal participants having blood pressure ≤ 120/80 mm Hg. with or without having antihypertensive medicines, to see whether microalbuminuria was happening due to impairment of glycemic status, chronicity of diabetes etc. It was found that microalbuminuria (estimated by Albumin: Creatinine Ratio, ie, ACR) was found to be worsen with the chronicity of DM and increased HbA1c level. ACR was positively and significantly correlated with age, chronicity and HbA1c level and showed negative significant correlation with Estimated Glomerular Filtration Rate (eGFR). eGFR was found to be significantly deteriorated with age, chronicity, uncontrolled glycemic status (HbA1c level) and Body mass index (BMI).

Key Words: ACR, BMI, diabetes mellitus, eGFR, HbA1c, T2DM.

INTRODUCTION

Apollonius of Memphis coined the term 'Diabetes' around 230 BC which means 'To pass through, a siphon' (Greek, 'Dia'= through, 'Betes'= to go). He considered diabetes as a disease of the kidneys and recommended the measures of bloodletting and dehydration. [1,2] In Latin, 'Mellitus' means honey or sweet. [2] Roman physician Galen explained diabetes as the weakness of the kidney and gave it the name 'Diarrhea urinosa'. [3]

DM is mainly of 4 types; [4,5] among which 90-95% of diabetic population belongs to type 2 diabetes mellitus (T2DM), [4-6] one of the world's most important non-communicable public health problems. [7] Insulin resistance (IR) [8,9] and relative insulin deficiency (not the primary deficiency of insulin) on later life is the main pathogenesis of T2DM. [4,7] T2DM is an extremely heterogeneous disease and no single cause can explain its natural history. [4,5] The underlying molecular defects (IR and insulin secretion) are a result of a combination of environmental and genetic factors. [4] Increased β-cell demand induced by IR is ultimately associated with progressive loss of β- cell function which is necessary for the development of fasting hyperglycemia. [4] The major defect is a loss of glucose-induced insulin release, which is termed as 'selective glucose unresponsive-ness' (glucotoxicity). [4] The degree of

dysfunction correlates with glucose concentration and duration of hyperglycemia and rapid restoration of euglycemia resolves the defect. [4] T2DM may be undetected for years and may appear as one of its dreaded complications; [4,5,7] so it may act as a 'hidden monster'. Undetected and/or uncorrected hyperglycemia for prolong duration leads to increased risk of developing microvascular and macrovascular complications. [7]

According to the diagnostic criteria of diabetes mellitus, HbA_{1c} ≥6.5% is considered to be diabetic and target limit of HbA1c of a diabetic patient on therapy is 7%. HbA1c between 5.7-6.4% is considered to be related to Impaired glucose tolerance or impaired fasting glucose (HbA1c to be measured in a laboratory using NGSP certified method, standardized to DCCT assay). [10]

Microalbuminuria is the reversible, earliest functional change of kidney in diabetic patients. [11] As a result of microvascular complications, diabetic nephropathy (DN) is the leading cause of end-stage renal disease (ESRD). [5] Prospective clinical studies document a strong relationship between hyperglycemia and the development of microvascular complications. [12,13] Hyperglycemia and IR both are responsible for macrovascular complications. [13,14] Four hypotheses have been proposed to explain the mechanisms of neural and vascular pathology due to hyperglycemia of prolonged duration: [i] increased aldose reductase (or polyol pathway) flux; [ii] enhanced formation of (Advanced glycation end products) AGEs; [iii] activation of protein kinase C; [iv] increased hexosamine pathway flux. [14,15] Pathogenesis and progression of diabetic nephropathy are the result of interactions between metabolic and hemodynamic pathways. AGEs, polyols (metabolic) and Renin- nagiotensin system, endothelin (hemodynamic)- all factors induce reactive oxygen species formation and thus changes in gene expression, modification of transcription and growth factors, cytokine liberations occur which ultimately produce structural (podocytopathy, damage of ECM, glomerulosclerosis) and functional (increased permeability, increased filtration and reduced reabsorption) changes. AGEs cross linked with the extracellular matrix (ECM) proteins causing damage to the glomeruli of basement membrane. Hence, proteinuria sets in DM. Microalbuminuria is associated with a two to fourfold increase in the risk of death in T2DM. [11] Control of blood glucose and blood pressure, particularly with angiotensin-converting enzyme (ACE) inhibitors, slow the rate of decline in renal function. [4,5] Annual estimation of ACR in all T2DM is recommended as one of the follow up investigations, starting from the 1st diagnosis of T2DM. [16]

Available literatures revealed that the prevalence of thyroid dysfunction in T2DM was 28.33% [17] and prevalence of microalbuminuria was 32.3% [18] at Bankura district, West Bengal, India. The present study was conducted with the aim to assess the relationship between glycemic status and renal functions. In this respect HbA1c, FPG, ACR, eGFR were measured among 125 tribal participants.

MATERIALS AND METHODS

A descriptive, cross-sectional, tertiary care hospital based study was conducted over a period of one and half year (March, 2016 to September, 2017) among 125 diagnosed case of T2DM patients from the Diabetic clinic of Bankura Sammilani Medical College and Hospital, Bankura (BSMCH) after getting the ethical clearance from the Institutional Ethics Committee, as per the inclusion and exclusion criteria. Systematic random sampling method was followed to obtain the 125 samples.

Inclusion criteria: Participants who spontaneously wished to take part in the study, normotensive (≤120/80 mm Hg.) with or without medicines, uncontrolled diagnosed cases of T2DM.

Exclusion criteria: Any acute or chronic debilitating diseases, patient was on any

therapy that may impair renal function, Patients having hypertension, tobacco abusers, patient on Angiotensin receptor blocker or Angiotensin Converting Enzyme Inhibitor (ARB/ACEI), patient who were albuminuric (excluded by urine dipsticks test), urinary tract infection or other acute infectious diseases.

The following tests were done at the department of Biochemistry, BSMCH: HbA1c, albumin concentration in urine, urinary and serum creatinine concentration. Thus, Albumin to Creatinine Ratio (ACR) of urine and eGFR were calculated by the following formula:

$$\text{ACR}\left(\frac{\text{mg}}{\text{g}}\text{of creatinine}\right) = \frac{\text{Albumin}\left(\frac{\text{mg}}{\text{dL}}\right)}{\text{Creatinine}\left(\frac{\text{g}}{\text{dL}}\right)} = \frac{\text{Albumin}\left(\frac{\text{mg}}{\text{dL}}\right)}{\text{Creatinine}\left(\frac{\text{mg}}{\text{dL}}\right)} \times 1000$$

eGFR= [186 X {Creatinine (mg/dL)} $^{-1.154}$ X (Age) $^{-0.203}$] X (0.742 if female) X (1.210 if black / African origin). [19,20]

BMI was calculated by the following formula after getting weight and height during examination of the participants:
BMI= Weight/ Height^2…… [Weight in kg; height in meter]

Table- 1: Stages of nephropathy according to albumin in urine

Stages	Dipstick test- urine protein	UAE (mg/ 24 hour)	AER (µg/ min)	Spot (random) urine sample	
				UAC (mg/L)	ACR (mg/g of creat)
Normoalbuminuria	Negative	< 30	< 20	< 20	< 30
Microalbuminuria	Negative	30–300	20–200	20–200	30–300
Macroalbuminuria	Positive	>300	>200	>200	>300

Table- 2: Stages of CKD

Stages	Description	eGFR (mL/ min/ 1.73 m^2)
1	Kidney damage with normal or increased eGFR	≥ 90
2	Kidney damage with mildly decreased eGFR	60–89
3	Moderately decreased eGFR	30–59
4	Severely decreased eGFR	15–29
5	Kidney failure	< 15

STATISTICAL METHODS

Data were codified and compiled in MS excel spread sheet and statistical analyses were done using a suitable statistical software (SPSS ver.20). Data were found to be skewed (examined by Shapiro Wilk test) and hence nonparametric tests were relevant to do. Appropriate statistical methods were applied to obtain central tendencies, significance of difference between means, cross tabulations and Chi-square tests between parameters, nonparametric test for correlation (Spearman's correlation) etc. were calculated and interpretations were done.

RESULTS

In the present study, 125 tribal participants suffering from uncontrolled T2DM were investigated, among whom female (count=69; 55.2%) outnumbered male counterpart (count=56; 44.8%).

Table- 3: Statistical distribution of different parameters

Attributes	Minimum	Maximum	Mean	SE of Mean	SD	Median
Age (years)	21	76	45.4	0.894	9.991	45.0
Chronicity of DM (years)	<1	24	4.67	0.421	4.702	3.0
BMI (kg/m^2)	19.83	40.36	28.53	0.311	3.476	28.34
HbA1c (%)	6.36	14.75	8.58	0.147	1.640	8.21
ACR (mg/g of creatinine)	12.650	288.338	57.554	5.843	65.328	28.226
eGFR (mL/min/1.73m^2)	35.44	156.01	73.986	2.109	23.583	72.39

Table- 4: Statistical parameters in between genders

Sex	Statistics	BMI (kg/m^2)	Age (years)	HbA1c (%)	ACR (mg/g of creatinine)	eGFR (mL/min/ $1.73m^2$)
Female (N=69)	Mean	29.374	43.29	8.788	53.892	67.060
	SD	3.399	8.713	1.789	61.223	19.792
Male (N=56)	Mean	27.489	48.00	8.326	62.066	82.520
	SD	3.309	10.89	1.409	70.357	25.204
Significance of difference in between sex (p value)		0.002	0.008	0.117	0.489	<0.001

Obesity was found to be significantly more in female than male counterpart. Males were more microalbuminuric but chronic deterioration of kidney function was better than female (as having better eGFR in male).

Table- 5: Cross tabulation between BMI groups and glycemic status (HbA1c)

BMI (kg/m^2)		HbA1c (%)	
		<7	≥7
18-24.99	Count (% within BMI group)	9 (52.9%)	8 (47.1%)
25-29.99		8 (10.8%)	66 (89.2%)
≥30		1 (2.9%)	33 (97.1%)
Pearson Chi-Square		<0.001	
Total		18 (14.4%)	107 (85.6%)

Uncontrolled glycemic status was significantly associated with higher BMI groups. 59.2% of participants were of overweight and 27.2% were belonged to obese.

Table- 6: Cross tabulation between groups of chronicity of DM and ACR groups

Chronicity of DM (years)		ACR (mg/g of creatinine)	
		<30	≥30
<3	Count (% within each chronicity of DM group)	64 (98.5%)	1 (1.5%)
3-5		18 (69.2%)	8 (30.8%)
5-10		4 (16.0%)	21 (84.0%)
≥10		0 (0.0%)	9 (100.0%)
Total	Count (% between ACR groups)	86 (68.8%)	39 (31.2%)

Pearson Chi-Square <0.001. Hence, deterioration of kidney functions was noted with the chronicity of diabetes mellitus.

Microalbuminuria (ACR≥30) was found in 31.2% of participants. 30.4% of females were found to be microalbuminuric whereas in male it was 32.1%.

It was found from statistical analysis that HbA1c levels were non-significantly but positively associated with ACR levels. When HbA1c<7%, only 16.7% of participants were having ACR≥30; whereas in HbA1c≥7%, ACR≥30 were found in 33.6% of participants.

Table- 7: Cross tabulation between eGFR groups and chronicity of DM, BMI, HbA1c

Category	Groups		eGFR (mL/min/$1.73m^2$)				Pearson Chi-Square
			<60	60-90	90-120	≥120	
Chronicity of DM (years)	<3	Count (% within Chronicity of DM group)	8 (12.3%)	27 (41.5%)	25 (38.5%)	5 (7.7%)	<0.001
	3-5		6 (23.1%)	18 (69.2%)	2 (7.7%)	0 (0%)	
	5-10		18 (72%)	7 (28%)	0 (0%)	0 (0%)	
	≥10		9 (100%)	0 (0%)	0 (0%)	0 (0%)	
BMI (kg/m^2)	18- 24.99	Count (% within BMI group)	2 (11.8%)	8 (47.1%)	6 (35.3%)	1 (5.9%)	0.027
	25-29.99		20 (27%)	36 (48.6%)	15 (20.3%)	3 (4.1%)	
	≥30		19 (55.9%)	8 (23.5%)	6 (17.6%)	1 (2.9%)	
HbA1c (%)	<7	Count (% within HbA1c group)	1 (5.6%)	11 (61.1%)	3 (16.7%)	3 (16.7%)	0.002
	≥7		40 (37.4%)	41 (38.3%)	24 (22.4%)	2 (1.9%)	
Total			41 (32.8%)	52 (41.6%)	27 (21.6%)	5 (4%)	-

Table- 8: Correlation table- Spearman's correlation

Spearman's Correlations		Age (years)	Chronicity of DM (years)	BMI (kg/m^2)	HbA1c (%)	ACR (mg/ g of creatinine)	eGFR (mL/min/$1.73m^2$)
Age	Correlation Coefficient	1.000	0.459	0.105	0.147	0.379	-0.460
	Significance (2-tailed)		<0.001	0.244	0.102	<0.001	<0.001
Chronicity of DM	Correlation Coefficient	0.459	1.000	0.068	0.070	0.796	-0.645
	Significance (2-tailed)	<0.001		0.454	0.437	<0.001	<0.001
BMI	Correlation Coefficient	0.105	0.068	1.000	0.745	0.139	-0.350
	Significance (2-tailed)	0.244	0.454		<0.001	0.121	<0.001
HbA1c	Correlation Coefficient	0.147	0.070	0.745	1.000	0.209	-0.413
	Significance (2-tailed)	0.102	0.437	<0.001		0.019	<0.001
ACR	Correlation Coefficient	0.379	0.796	0.139	0.209	1.000	-0.597
	Significance (2-tailed)	<0.001	<0.001	0.121	0.019		<0.001
eGFR	Correlation Coefficient	-0.460	-0.645	-0.350	-0.413	-0.597	1.000
	Significance (2-tailed)	<0.001	<0.001	<0.001	<0.001	<0.001	

DISCUSSION

Hyperglycemia is the hallmark of DM and HbA_{1c} is the important diagnostic as well as prognostic marker of DM, by which we can assess the glycemic condition of a patient over a period of about 2-3 months.

Obesity is one of the major factors in the pathogenesis of DM (producing insulin resistance) and has a central role to produce different types of complications. [4,5] In present study, obesity (measured by BMI) was found to be related to chronicity of DM as well as glycemic status. In the same context it was worth to mention that in present study, BMI groups were significantly related to the eGFR groups, meaning that rising trend of BMI might lead to compromise the renal function. A study supported the fact that increased BMI was found to deteriorate renal function. [21]

It was clear from the statistical analyses of present study that renal function had a downward trend with increasing age and chronicity of T2DM. It was found that eGFR was deteriorating more in females with respect to males. Microalbuminuria was found altogether in 31.2% of population with very slight preponderance to male participants. ACR had highly significant positive correlation with age, duration of DM, HbA1c and significant negative correlation with eGFR. The prevalence of microalbuminuria was found 32.3% (in male 37.5% and in female 62.5%) in T2DM, in a previous study. [18] The National Health and Nutrition Examination Survey (1999 to 2006) showed that the prevalence of microalbuminuria increases as glycaemia worsens, i.e., from 6% in normoglycaemia, to 10% in impaired fasting glucose and 29% in diabetes cases. [22] Microalbuminuria was found to be associated with insulin resistance and might produce T2DM. [23]

In present study it was seen that eGFR had a linear negative correlation with HbA_{1c}; i.e., uncontrolled DM deteriorated kidney function. In previous studies it was stated that HbA_{1c} was used to evaluate the degree of metabolic control in diabetics and to predict the risk of vascular complications. [24] Study by Takenouchi et al. reflected a direct association between HbA_{1c} variability and kidney function decline in T2DM and this association was found to be stronger in patients with microalbuminuria than in normoalbuminuria. [25]

CONCLUSION

Gradual and sustained deterioration of kidney function was seen in T2DM but in microalbuminuric phase it could be revert back by stringent control of hypertension and hyperglycemia and thus could halt the progress to diabetic nephropathy. Chronicity of diabetes and uncontrolled glycemic status and excess weight (increased BMI) could worsen renal function. Angiotensin Converting Enzyme Inhibitor or Angiotensin Receptor Blocker could be the mainstay of treatment, if not contraindicated, to control hypertension as well as to support the kidney from deterioration.

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