

## "Significance of Microalbuminuria in Newly Diagnosed type 2 Diabetes Mellitus"

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### **Abstract:**

**Background:** Microalbuminuria is considered as the earliest clinical evidence of diabetic nephropathy at which appropriate intervention can retard, or reverse, the progression of the disease including microvascular and microvascular complications of diabetes. Without specific interventions, 20–40% of type 2 diabetic patients with Microalbuminuria progress to overt nephropathy.

### **Aims and objectives of the Study:**

To assess the incidence of microalbuminuria in newly diagnosed type 2 diabetes and to identify the risk factors for nephropathy.

**Study Place And Duration:** The present study was conducted at the Department Medicine in collaboration with Diabetic clinic, Assam Medical College, during the period of 1<sup>st</sup> July 2012 to 30<sup>th</sup> June, 2014.

**Study Design:** Cross sectional study

**Methods:** We studied 104 newly diagnosed Type 2 Diabetes mellitus patients for detection of Microalbuminuria by Micral Test (dipstick) method in a random spot urine sample. Microalbuminuria was diagnosed if the urinary albumin excretion was >30 mg/g of creatinine.

**Results:** The overall incidence of microalbuminuria was 20.19%. There was significant association of microalbuminuria with the increase in duration of diabetes, high blood pressure, increase BMI, high glycated haemoglobin, high post-prandial plasma glucose, and Lipid profile especially with high total cholesterol and LDL.

**Conclusion:** Implementing effective interventions for better control of these risk factors in type 2 diabetic patients may lower their risk for diabetic nephropathy and further impending complications of Diabetes.

**Keywords:** Microalbuminuria; Type 2 diabetes Mellitus

### **I. Introduction**

Diabetes has become a major cause of morbidity and mortality throughout the world especially more alarming in developing countries as it's effect on economy is profound in the 21<sup>st</sup> century. The prevalence of diabetes has increased rapidly over the past several decades<sup>1</sup>. Type 2 diabetes constitutes about 85% to 95% of all diabetes cases in developed countries and accounts for an even higher percentage in developing countries<sup>2</sup>.

India leads the global top ten in terms of the highest number of people with diabetes, with a figure of 50.8 million for 2010<sup>2,3</sup>. One of the most severe complications of diabetes is the development of Diabetic Nephropathy and it is the leading cause of end-stage renal disease (ESRD) worldwide. Nearly 30% of chronic renal failures in India are due to diabetic nephropathy.<sup>4,5,6</sup> Kidney disease (Diabetic Nephropathy) in diabetic patients is clinically characterized by increasing rates of urinary albumin excretion, starting from normoalbuminuria, which progresses to Microalbuminuria, Macroalbuminuria and eventually to ESRD.

Without specific interventions, 20–40% of type 2 diabetic patients with Microalbuminuria progress to overt nephropathy<sup>7</sup>. In diabetic patients with Proteinuria, the relative mortality is about 40 times higher than in diabetics without Proteinuria. It is estimated that death due to renal disease is 17 times more common in diabetics than in nondiabetics<sup>8</sup>. Racial differences in the prevalence of diabetic renal disease have been reported. Asian subjects have significantly higher prevalence (52.6%) of diabetic end stage renal disease (ESRD) when compared with the Caucasians (36.2%). The results of several studies suggest that the incidence and prevalence of nephropathy in type 2 diabetes mellitus (type 2 DM) differ between geographical locations and ethnic groups, with Mexican-Americans, Pima Indians, people of African descent, and Asians being particularly at risk.<sup>9,10,11,12</sup>

Thus, Microalbuminuria is a major risk factor for renal and cardiovascular events, and the early identification and treatment of patients at increased risk for Microalbuminuria may be instrumental to limit the excess renal and cardiovascular disease associated with type 2 diabetes. Attempts at prevention of nephropathy in type 2 DM have focused on the prevention of Microalbuminuria, the earliest clinical hallmark of nephropathy, or its progression to macroalbuminuria.<sup>13,14</sup>

According to the American Diabetes Association position statement (2009) recommendations for nephropathy screening and treatment, urine albumin excretion should be tested annually in all type 2 diabetic patients, starting at diagnosis.<sup>15</sup>

The implementation of routine screening for renal disease is still far below recommended goals in India.<sup>16</sup> There's limited study data available on Microalbuminuria and its relations with clinical profiles of newly diagnosed Type 2 Diabetes mellitus in India. In North-East India, there are related data available which are only restricted to few unpublished reports. Therefore, the present study made an attempt to look at the albumin excretion levels (microalbuminuria) in relation to risk factors in newly diagnosed type 2 DM patients with the aims and objectives as stated below:

**Aims and objectives of the Study:** To assess the incidence of microalbuminuria in newly diagnosed type 2 diabetes and to identify the risk factors for diabetic nephropathy.

**Type Of Study:** Cross sectional study,

**Sample Size And Type:** All the cases of newly diagnosed type 2 diabetes mellitus who had attended and/or were admitted in the Department of Medicine and Diabetic Clinic, Assam Medical College and Hospital, Dibrugarh were taken up for the study.

After considering the inclusion and exclusion criteria, a total number of 104 cases were taken up for the study.

## II. Selection Criteria

### **Inclusion Criteria:**

1. Newly diagnosed Type 2 Diabetes mellitus (Newly diagnosed-arbitrary fixed at or < 6 months)<sup>17</sup>
2. Age at or above 20 yrs.<sup>18</sup>

### **Exclusion Criteria:**

1. Patients' age less than 20 years,<sup>18</sup>
2. Patients' of Type 2 Diabetes Mellitus already diagnosed with or without treatment of > 6 months,
3. Diabetes mellitus other than Type 2 Diabetes mellitus,
4. Primary and secondary renal diseases,
5. Diagnosed cases of Overt Nephropathy of any etiology,
6. Patient's having Confounding Factors like Fever, pregnancy, women in Menstrual period, Urinary tract Infections, Congestive Cardiac failure etc,
7. Hypertensive Patients with BP  $\geq$  160/100 mmHg<sup>19,20</sup>
8. Hypertensive patients on Angiotensin Converting enzyme inhibitors (ACE Inhibitors/Angiotensin Receptor Blockers (ARBs))<sup>19,20</sup>

### **Case Definitions:**

**a. Diabetes** was diagnosed as per guidelines stated by American Diabetic Association diagnostic Criteria, 2012<sup>21</sup>.

#### **b. Type 2 Diabetes Mellitus:**

It was diagnosed empirically by the absence of features suggesting Type 1 diabetes and of any other conditions that cause hyperglycemia.<sup>22</sup> Age was not used as criteria to differentiate between type 1 and type 2 diabetes. As type 2 diabetes is being increasingly reported in younger age group<sup>22</sup>, cases of 20 years and above were taken up in study<sup>18</sup>. Fasting C peptides were done in cases where there was doubt in differentiating type 1 and type 2 diabetes.<sup>23</sup>

#### **c. Newly Diagnosed Type 2 Diabetes Mellitus:**

A case of Type 2 DM diagnosed within last 6 months of presentation were arbitrarily considered as Newly diagnosed type 2 diabetes. The duration of diabetes was enquired and confirmed with the reports of the first diagnostic values.<sup>24</sup>

#### **d. Blood sugar Control was graded based on HbA1c<sup>25</sup> level as follows:**

- Good control: HbA1C <7%
- Fair Control: HbA1C 7-7.99%
- Poor Control: HbA1c  $\geq$ 8%

**e.BMI(Body Mass Index):**<sup>26,27</sup>

BMI was measured by the formula of dividing weight in Kgs by height in meter square.

Ministry's consensus guidelines for the Prevention and Management of Obesity and Metabolic Syndrome, India 2008 guidelines were followed for classification which is as follows:

BMI(Kg/m <sup>2</sup> )	CATEGORY
≤18.4	Underweight
18.5-22.9	Normal
23-24.9	Over weight
> 25	Obese

**f.Smoker:** Smokers were defined as those currently smoking or having smoked one or more cigarettes per day for >1 yr.<sup>28</sup>

**g.Alcohol Consumption:** Alcohol Consumption was defined by the number of drink units consumed per week (a drink unit is 285 ml beer or larger, 115 ml wine or 25 ml liquor).<sup>28</sup>

**Estimation of Microalbuminuria by Micral test:**

All patients having macroalbuminuria were excluded from the study. Micral test, an immunological rapid dip stick semi qualitative technique for detection of Microalbuminuria, was used for estimation of microalbuminuria.

The Micral-Test is used to measure urinary albumin in the range 20-200 mg/l (microalbuminuria). It is a semi-quantitative test for the detection of microalbumin in urine.

**Specimen:** The test was conducted in random spot collected urine sample in a clean reservoir. Strenuous physical activity was avoided within 24 hour of specimen collection. Specimen was not collected from patient with acute febrile illness, menstruating women and those having hematuria.

**Micral Test:**

**Reagent Composition:**

Each Urine Test Strip contains Monoclonal Antibodies: Anti-human albumin IgG labeled with colloidal gold (6µg/cm<sup>2</sup>) and Fixed albumin (9.5 µg/cm<sup>2</sup>).

**Test Principle:**

The albumin present in the urine specifically binds with a soluble antibody-gold conjugate present on a zone on the test strip. Excess conjugate is retained in a separation zone containing immobilized human albumin. This allows only the conjugate-albumin immunocomplex from the sample to reach the detection zone. After one minute, the intensity of the color produced (white to red) is directly proportional to the albumin content in the urine.

**Test Procedure:**

1.The test strip was dipped into the urine for 5 seconds. The urine level was kept in between the two black lines. The strip is then withdrawn carefully to avoid it touching the sides of the collection cup.

2.The strip was then placed on a nonabsorbent surface or across the top of the collection cup to allow excess urine to drain.

3.After approx. 1 minute, the color of the test pad was matched above the inscription "MICRAL" with the color scale on the test strip vial.

**N:B:** Comparison of the color reaction with the color scale is possible for up to 5 minutes only, and then the color disintegrates.

**Statistical Analysis:**

The statistical analysis was carried out using Statistical Package of Social Science (SSPS Inc., Chicago, IL, version 20.00 for window, 2011).

All quantitative variables were estimated using measures of central tendency (mean, median) and measures of dispersion. Chi square test and Fischer's exact tests were used to compare frequencies as

appropriate. Student's t test was used to compare means between two groups. p value was considered significant at a level of < 0.05.

### III. Results

The study sample consisted of 104 cases, out of these, 62(59.61%) and 42(40.39%) were males and females respectively. The overall incidence of microalbuminuria was 20.19%. The incidence of Microalbuminuria is more common in males (69.90 %) than in females (38.10%).

A total of 84 patients (80.76%) were on treatment with oral hypoglycemic and 19 patients (18.26%) were on treatment with Insulin whereas 4 patients (3.84%) were on both insulin and oral hypoglycemic drugs therapy. Age of patients at diagnosis ranged between 28 to 85 years. The maximum number of patients (61%) was clustered between 40 to 59 yrs of age. The mean age of detection of diabetes mellitus among the male patients was 52.03 ± 12.49 years and in that of female patients was 48.78 ± 9.97 years respectively.

**Table-1: Distribution Of Patients' In Relation To Urinary Albumin Excretion Level**

ALBUMIN EXCRETION LEVEL	NUMBER (n)	PERCENTAGE (%)
NORMOALBUMINURIA	83	79.80
MICROALBUMINURIA	21	20.19
TOTAL	104	100

The above data shows that 20.19% (n=21) patients had microalbuminuria and the remaining 79.8% patients (n=83) were found to be negative for microalbuminuria.

**Table-2: Distribution Of Patients' In Relation To Duration Of Diabetes Mellitus Since Diagnosis**

DURATION OF DM (in months)	MALE		FEMALE		TOTAL	
	n	%	n	%	n	%
< 2	24	23.07	12	11.53	36	34.6
2—<4	18	17.30	15	14.42	33	31.72
4—6	20	19.23	15	13.46	35	32.69
TOTAL	62	59.61	42	40.38	104	100
Mean ± S.D.	2.68 ± 1.70 months		2.88 ± 1.50 months		2.78 ± 1.60 months	
Range	1—6 months		1—6 months		1—6 months	

The maximum number of microalbuminuric patients (57.14% out of 21 microalbuminurics) were in the 4 to 6 months group since diagnosis. There's significant correlation between duration of diabetes and microalbuminuria (P <0.05).

**Table-3: Age Distribution In Relation To Urinary Albumin Excretion Level**

AGE	NORMOALBUMINURIA		MICROALBUMINURIA		TOTAL	'P' VALUE
	n	%	n	%		
20—29	1	.96	0	0	1	>0.05
30—39	18	85	3	14.28	21	
40—49	23	79.31	6	20.68	29	
50—59	26	81.25	6	18.75	32	
60—69	11	73.33	4	26.66	15	
≥70	4	66.66	2	33.33	6	
TOTAL	83		21		104	

The maximum number of patients (57.64%) were clustered between 40-59 yrs of age. Mean age (in yrs) of detection was found to be 49.48±11.90. There's no patient above 85 years.

**Table-4: Hba1c With The Incidence Of Urinary Albumin Excretion Level**

HbA1c (%)	NORMOALBUMINURIA		MICROALBUMINURIA		TOTAL	'P' VALUE
	n	%	n	%		
<7 %	31	96.87	1	3.12	32	<0.05
7—7.99%	22	73.33	8	26.66	30	
≥ 8%	30	71.42	12	28.57	42	
TOTAL	83		21		104	

The above data shows the maximum number of (57.14%) microalbuminurics were seen when the HbA1c level >8% and it's statically significant. (P<0.05).

**Table-5: Body Mass Index (Bmi) In Relation To Urinary Albumin Excretion Level**

Body Mass Index	NORMOALBUMINURIA	MICROALBUMINURIA	P VALUE
Male	24.64±2.69	26.15±3.70	0.0371
Female	23.77±2.6	25.25±3.27	0.0313

The above data shows that the BMI was more in microalbuminurics than normoalbuminurics in both male and females. The difference was found to be statically highly significant both in males and females (P=0.036 & 0.029 respectively).

**Table-6: Lipid Profile With The Incidence Of Urinary Albumin Excretion Level**

LIPID PROFILE		NORMOALBUMINURIA	MICROALBUMINURIA	P VALUE
CHOLESTEROL		171.39±38.94	195.57±48.84	0.017
LDL-C		101.99±32.50	124.76±44.17	0.009
Triglyceride		145.71±44.18	161.48±48.42	0.154
HDL	MALE	35.78±5.98	37.45±3.64	0.224
	FEMALE	46.37±5.59	42.50±11.59	0.0294

The mean of total Cholesterol, LDL cholesterol, and Triglycerides level were higher in microalbuminurics than normoalbuminuric group. The differences were statically highly significant except in HDL (in males) and triglycerides level (P=0.154 & P.0.224).

**Table-7: Mean Blood Sugar Parameters In Relation To Urinary Albumin Excretion Level**

BLOOD SUGAR	NORMOALBUMINURIA	MICROALBUMINURIA	'P' VALUE
RBS (mg/dl)	260.06±96.31	295.14±107.05	0.14
FBS (mg/dl)	202.61±87.21	230.81±111.66	0.21
PPBS (mg/dl)	286.32±115.55	362.24±143.02	0.01

The mean of random, fasting and post-prandial blood sugar level were higher in microalbuminuric group than normoalbuminuric group. The difference was found to be statically significant in post-prandial blood sugar level only ((P=0.01).

**Table-8: Mean Blood Pressure In The Relation To Urinary Albumin Excretion Level**

BLOOD PRESSURE	NORMOALBUMINURIA	MICROALBUMINURIA	'P' VALUE
SBP (mmHg)	127.59±10.047	131.628.64	0.09
DBP(mmHg)	77.36±5.801	80.95±4.31	0.009

The mean SBP and DBP both were found to be in linear relationship with the urinary albumin excretion level and they were statically highly significant as well (P=0.09 & 0.009).

**Table-9: Smoking, Alcohol And Family History With The Incidence Of Albumin Excretion Level**

FACTORS	NORMOALBUMINURIA	%	MICROALBUMINURIA	%	n	'P' VALUE
Smoking	20	74.07	7	25.92	27	>.05
Alcohol	24	80	6	20	30	
Family History	17	80.95	4	19.04	21	

Patients' who had history of smoking, alcohol consumption and family history were found to be not statically significant in comparison to microalbuminurics than non-microalbuminuric group (P >0.05).

**Table-10: Clinical and biochemical characteristics of the Study Population**

Characteristics	Normoalbuminuria	Microalbuminuria	P VALUE
AGE	48.55±11.20	53.14±14.03	0.11
DURATION(months)	2.54±1.572	3.62±1.532	0.005
RBS	260.06±96.311	295.14±107.05	0.14
FBS	202.61±87.219	230.81±111.66	0.21
PPBS	286.32±115.556	362.24±143.02	0.01
BMI	24.31±2.69	25.72±3.448	0.04
HbA1C	7.833±1.6822	8.8948±2.38	0.02
CHOL	171.39±38.94	195.57±48.84	0.01
LDL	101.99±32.508	124.76±44.175	0.009
TGL	161.48±48.429	145.71±44.183	0.15
HDL	40.12±8.126	39.67±8.002	0.08
S. Creatinine (mg/dl)	.89±.09	1.08±.18	0.01

#### IV. Discussion

Several worldwide studies have reported the incidence of Microalbuminuria in newly diagnosed Type-2 DM patients, which varies widely (15-54%).

AUTHOR	SOURCE	YEAR	PREVALENCE (%)
1. Viberti et al <sup>29</sup>	Diabetes Care (ADOPT STUDY)	2002	15.2
2. Sosenko et al <sup>30</sup>	Diabetes Care (The Strong Heart Study)	2002	18
3. Niskanen et al <sup>31</sup>	Diabetologia	1990	19
4. Debbarma et al	IOSR-JDMS	2015	20.19
5. Vijay et al <sup>32</sup>	INT. J. DIAB. DEV. COUNTRIES	1998	21
6. Yajnik et al <sup>33</sup>	Diab. Res. and Clin. Prac	1992	23
7. Annemieke et al <sup>34</sup>	Diabetes Care (The Hoorn Screening Study)	2003	26.7
8. Cathelineau et al <sup>35</sup>	Metabolism (Diadem Study)	1997	29.6
9. Unuigbo et al <sup>24</sup>	Afr J Med Med Sci.(MEDLINE)	2004	49.2
10. Bhashkar et al <sup>17</sup>	NJJIRM (Nat. J. Integtd. Res. Med.)	2011	54.09

This variation in prevalence can be attributed to factors such as differences in populations, in the definitions of Microalbuminuria, method of urine collection, etc. However this could also reflect true differences in the ethnic susceptibility to nephropathy. The microalbuminuric patients were older and had a longer duration of diabetes (57.14%) in comparison to normoalbuminuric group (p<0.001).

The microalbuminuric patients had significantly increased systolic and diastolic blood pressure compared to normoalbuminuric subjects (p<0.01). Plasma glucose specially post-prandial glucose level and HbA1c concentrations were significantly higher in the microalbuminuric group compared with the normoalbuminuric subjects (p<0.001).

Mean BMI of microalbuminuric patients was  $25.72 \pm 3.448 \text{ kg/m}^2$  and for normoalbuminuric patients it was  $24.31 \pm 2.69 \text{ kg/m}^2$ . So its obvious that patients with a body mass index of more than  $25 \text{ kg/m}^2$  have significant increase in the incidence of Microalbuminuria. An HbA1c value above 8% is associated with 44% incidence of Microalbuminuria. Serum total cholesterol and LDL values were significantly increased in both groups but triglyceride level is not statically significant.

Our study revealed that obesity, duration of diabetes, high blood pressure, post- prandial blood sugar, HbA1c and dyslipidemia(total cholesterol, LDL, and HDL) as the risk factors for Microalbuminuria.

Gupta et al<sup>167</sup> reported HbA1c to be associated with Microalbuminuria, John et al<sup>19</sup> reported male sex, older age, longer duration of diabetes, poor glycaemic control, and raised blood pressure as risk factors of Microalbuminuria, while Vijay et al<sup>20</sup> reported duration of diabetes, systolic and diastolic blood pressure, age of the patient, and serum creatinine to be associated with proteinuria. Age was reported as one of the risk factors in the Wisconsin study,<sup>25</sup> in Danish population study,<sup>26</sup> and also in the Pima Indians.<sup>27</sup> The association of glycaemic control with Microalbuminuria has been well established by various studies.<sup>25,27,36</sup> Other factors which are reported to be associated with Microalbuminuria are alcohol intake,<sup>25</sup> and smoking.<sup>37</sup> but our study didn't find any significant association which might be due to less smoking and drinking habits in the study population in comparison to that of western or other parts of the world.

#### V. Conclusion

Microalbuminuria screening test is cost-effective and easy to perform, thus it will help to relieve some of the burden on our health care system, at the same time, physicians may be able to prevent progressive renal disease, and ultimately renal failure, in many patients with diabetes.

The current study showed several positive attributes e.g Obesity, poor glycaemic control, Age, high BP, longer duration of diabetes and dyslipidemia are associated Microalbuminuria in newly diagnosed Type 2 DM.

The risk factors identified in the present study are similar to those reported in the literature. As we know that there is high prevalence of diabetes in India with over 20 million diabetics already and the numbers expected to increase to 57 million diabetics by the year 2025, this could place considerable burden on the health

budgets of this country. This calls for early detection and good control of diabetes to reduce the burden of diabetic kidney disease in the future.

Implementing effective interventions for better control of these risk factors in type 2 diabetic patients may lower their risk for developing diabetic nephropathy and further impending complications of Diabetes.

We recommend screening of Microalbuminuria at diagnosis as per ADA guidelines and periodic evaluation of urine albumin in addition to HbA1C in patients with newly diagnosed Type 2 diabetes mellitus.

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