10.5005/jp-journals-10045-0046

ORIGINAL ARTICLE

Study of Association between Microalbuminuria and Microvascular Complications in Type II Diabetes Mellitus Patients in RajaRajeswari Medical College and Hospital, Karnataka

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ABSTRACT

Introduction: India is claimed to be the diabetes capital of the world. Many studies had proven that persistent hyperglycemia and associated metabolic syndrome features like hypertension, dyslipidemia, and obesity contribute to the development of vascular complications. The risk of chronic complications increases as a function of the duration of hyperglycemia; they usually become apparent in the second decade of hyperglycemia. Since type II diabetes mellitus (DM) often has a long asymptomatic period of hyperglycemia, many individuals with type II DM have complications at the time of diagnosis. The vascular complications of DM are subdivided into microvascular (retinopathy, neuropathy, nephropathy) and macrovascular (coronary artery disease, peripheral arterial disease, cerebrovascular disease) complications. The present study aims to study the occurrence of microalbuminuria in patients with type II DM and note its association with the duration of diabetes since diagnosis and microvascular complications of DM.

Study design: Prospective observational study.

Materials and methods: The study is a clinical, prospective, and observational study of 100 type II diabetics attending the medicine department outpatient/inpatient of RajaRajeswari Medical College & Hospital, Bengaluru, Karnataka, India, who form the subjects for the study conducted from August 2015 to July 2016 (12 months) and who matched the inclusion criteria.

Data were collected after obtaining informed/written consent from patient. After detailed history, detailed clinical examination, and general physical and systemic examinations, fundoscopy was carried out and relevant laboratory investigations were done.

Results and conclusion: The overall occurrence of microalbuminuria was 38%. The occurrence of microalbuminuria showed a direct relationship with increasing age (p = 0.053) and increasing duration of diabetes since diagnosis. A hemoglobin (Hb)A1c value above 7% is associated with 50% or higher incidence of microalbuminuria (p = 0.018). Patients with a body mass index of more than 25kg/m2 have increased risk of developing type II DM and significant increase in microalbuminuria. The incidence of microalbuminuria is significantly associated with the presence of retinopathy (p = 0.061), peripheral neuropathy (p = 0.009), and hypertension (p ≤ 0.001). Microalbuminuria is inversely associated with high-density lipoporotein (p = 0.089). During the evaluation of diabetic patients and the occurrence of microalbuminuria, the possibility of microalbuminuria and its correlation with various complications of DM should be kept in mind.

Keywords: Incipient diabetic nephropathy, Microalbuminuria, Type II diabetes mellitus.

How to cite this article: Bhavya N, Kumar VA. A Study of Association between Microalbuminuria and Microvascular Complications in Type II Diabetes Mellitus Patients in RajaRajeswari Medical College and Hospital, Karnataka. J Med Sci 2017;3(1):6-10.

Source of support: Nil

Conflict of interest: None

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INTRODUCTION

Diabetes mellitus (DM), the most common endocrine disorder, is characterized by metabolic abnormalities and long-term microvascular and macrovascular complications. The prevalence of diabetes is on the rise, and is more alarming in the developing countries. Besides increasing the risks for coronary heart disease, diabetes enhances the incidences of cerebrovascular accidents too. Moreover, it is the leading cause of acquired blindness and accounts for about a quarter of the cases with end-stage renal diseases as well as half of the cases of nontraumatic lower limb amputations.

Diabetic nephropathy occurs in as many as 30% of insulin-dependent DM patients and 25% of noninsulin-dependent DM patients. Diabetic nephropathy is a dreaded disease with progressive and continuous deterioration in glomerular function resulting in irreversible renal failure. Diabetic nephropathy is an important cause of morbidity and mortality and is now among the most common cause of end-stage renal disease. However, there is an early phase of diabetic renal disease called incipient diabetic nephropathy. In this stage, there is a rise in urinary excretion of albumin, i.e., microalbuminuria. But, the rise is detectable only by the use of sensitive assays for urinary albumin.

Microalbuminuria is an important warning sign for both the physician and the patient, which, if ignored, can

lead to an irreversible renal damage. Microalbuminuria is most commonly associated with other microvascular complications of diabetes, namely retinopathy, neuropathy, and ischemic heart disease. So, microalbuminuria may be a maker for widespread microvascular damage in a patient with DM.

In the current study, we intend to study the occurrence of microalbuminuria in patients with noninsulin-dependent DM and also find out its association with the duration of DM and the microvascular complications of DM.[1,2]

MICROVASCULAR COMPLICATIONS

- Eye disease – Retinopathy (proliferative/nonproliferative), macular edema, cataract
- Neuropathy – Sensory and motor (mono and poly neuropathy), autonomic neuropathy
- Nephropathy.[3-5]

MICROALBUMINURIA

This term denotes a significant increase in albumin excretion rate. Albumin excretion in healthy individuals ranges from 1.5 to 20 µg/min with geometric mean in the range of 6.5 µg/min. These values have been termed as normoalbuminuria. Microalbuminuria, thus, defines the wide substantial range of hypersecretion of albumin, ranging between 20 and 200 µg/min.[7] Normal persons excrete less than 30 mg/day of albumin. Microalbuminuria is not detected by reagent sticks for urinary protein, which generally become positive only when protienuria is greater than 550 mg/day. This degree of leakage is termed as macroalbuminuria.[5]

Definition of Microalbuminuria and Clinical Nephropathy[6]

Term	*Synonym*	*Urinary albumin level*
Normoalbuminuria		<20 µg/ min
Microalbuminuria	Incipient nephropathy	20–200 µg/min or 30–300 mg/24 hrs
Macroalbuminuria	Clinical/overt nephropathy	≥200 µg/min or ≥300 mg/24 hrs

MATERIALS AND METHODS

A total of 100 patients with noninsulin-dependent DM admitted to RajaRajeswari Medical College & Hospital, Bengaluru, Karnataka, India, were studied. The patients were taken from the medical wards of the hospital based on random selection. Patients were considered to be diabetic based on American Diabetic Association (ADA) criteria for diagnosis of DM, which is

- Symptoms of DM plus a random glucose concentration ≥200 mg/dL (11.1 mmol/L). The classic symptoms of DM include polyuria, polydipsia, and unexplained weight loss.

  OR
- Fasting blood glucose ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 hours.

  OR
- 2-hour postprandial glucose ≥200 mg/dL (11.1 mmol/L). Among diabetics, the above criteria were considered for the inclusion of the patients for the study.

Inclusion Criteria

- The ADA criteria for Type II DM.[5]

Exclusion Criteria

- Patients with macroalbuminuria
- Patients with congestive cardiac failure, urinary tract infection
- Ketonuria
- Pregnant patients
- Patients with overt diabetic nephropathy
- Patients with preexisting renal disease

The selected patients were studied in detail with history and physical examination.

History

- Patients' characteristics, such as age, sex, age of onset, and duration of diabetes.
- All details regarding the present complaints were noted.
- Total duration of diabetes, the drugs the patient was taking, and the dosages were noted. The regularity of the treatment taken by the patients was also noted. The family history regarding diabetes was taken.
- Personal history regarding smoking, alcohol consumption, bowel and bladder habits, and drug intake was noted.

A complete clinical examination was carried out in each patient with particular reference to the complications of diabetes like retinopathy, neuropathy, and nephropathy. Height and weight were measured in all cases and body mass index (BMI) was calculated by weight in kg/height in m^2.

Hypertension was said to be present when there was a history of hypertension or systolic blood pressure was recorded greater than 160 mm Hg and/or diastolic pressure was greater than 90 mm Hg on three consecutive occasions. Peripheral neuropathy was judged to be present if there was historical evidence of neuropathic pain, numbness or tingling sensation in the extremities, or absence of ankle jerks along with diminished vibratory threshold or pinprick sensation in hands or feet

on examination. Fundus examination was done in all patients for evidence of diabetic retinopathy. Retinopathy was said to be present when there was evidence of microaneurysm, soft or hard exudates, and hemorrhages. Neovascularity was considered as evidence for proliferative retinopathy.

The following investigations were done in all the patients.

- Microalbuminuria was estimated by Turbilatex test
- Fasting blood sugar (FBS) and postprandial blood sugar (PPBS)
- Glycosylated hemoglobin
- Blood urea and serum creatinine
- Fasting lipid profile
- Urine routine and culture
- Electrocardiogram, echocardiography
- Carotid Doppler and nerve conduction studies

Estimation of Microalbuminuria by Latex Turbidometric Test

Latex particles coated with specific antibodies, such as antihuman albumin are agglutinated when mixed with samples containing microalbumin. The agglutination causes an absorbable change, dependent on the microalbumin contents of the patient sample that can be quantified by comparison from a calibrator of known microalbumin concentration. Sensitivity of the assay and the target value of the calibrator have been standardized against the international reference material CRM470/RPPHS.

Specimen Collection

All patients were afebrile during the course of collection of urine and were kept at rest during the collection of urine. The first morning midstream urine sample was collected in a sterile container. Urine of the patient was first tested for albumin by albustix method. Patients who were negative for albumin by the albustix method were only included in this study.

Microalbuminuria was graded as follows:

- Mild (20–50 mg/L) = +
- Moderate (50–100 mg/L) = ++
- Severe (100–300 mg/L) = +++

Severity of diabetes was graded based on hemoglobin (Hb)A1c levels as follows:

- Mild: <7.0%
- Moderate: 7.0 to 7.5%
- Severe: >7.5%

Blood urea, serum creatinine, and lipid profile were estimated in all cases.

RESULTS

The results are tabulated from Tables 1 to 7.

DISCUSSION

Type II DM is being increasingly recognized as a disease, which is characterized by dysfunction of the endothelium. Endothelial dysfunction occurs in a generalized and widespread manner in diabetic subjects. The severity of the dysfunction is directly proportional to the age of the

Table 1: Age distribution of patients studied

	Gender		
Age in years	*Female*	*Male*	*Total*
31–40	8 (18.6%)	10 (17.5%)	18 (18%)
41–50	10 (23.3%)	16 (28.1%)	26 (26%)
51–60	15 (34.9%)	15 (26.3%)	30 (30%)
61–70	8 (18.6%)	13 (22.8%)	21 (21%)
71–80	2 (4.7%)	3 (5.3%)	5 (5%)
Total	43 (100%)	57 (100%)	100 (100%)

p = 0.911, not significant, Fisher exact test

Table 2: Age distribution of patients studied in relation to incidence of microalbuminuria

	Microalbuminuria		
Age in years	*Absent*	*Present*	*Total*
31–40	14 (22.6%)	4 (10.5%)	18 (18%)
41–50	18 (29%)	8 (21.1%)	26 (26%)
51–60	19 (30.6%)	11 (28.9%)	30 (30%)
61–70	10 (16.1%)	11 (28.9%)	21 (21%)
71–80	1 (1.6%)	4 (10.5%)	5 (5%)
Total	62 (100%)	38 (100%)	100 (100%)

p = 0.095$^+$, significant, Fisher exact test

Table 3: Age of onset of DM of patients studied in relation to incidence of microalbuminuria

Age of onset of DM	*Microalbuminuria*		
	Absent	*Present*	*Total*
30–50	38 (61.3%)	20 (52.6%)	58 (58%)
50–60	17 (27.4%)	15 (39.5%)	32 (32%)
60–70	7 (11.3%)	3 (7.9%)	10 (10%)
Total	62 (100%)	38 (100%)	100 (100%)

p = 0.439, not significant, Chi-square test

Table 4: The BMI (kg/m^2) distribution of patients studied in relation to incidence of microalbuminuria

	Microalbuminuria		
BMI (kg/m^2)	*Absent*	*Present*	*Total*
<18.5	3 (4.8%)	2 (5.3%)	5 (5%)
18.5–25	50 (80.6%)	23 (60.5%)	73 (73%)
25–30	6 (9.7%)	7 (18.4%)	13 (13%)
>30	3 (4.8%)	6 (15.8%)	9 (9%)
Total	62 (100%)	38 (100%)	100 (100%)

p = 0.109, not significant, Fisher exact test

Table 5: Blood sugar distribution of patients studied in relation to incidence of microalbuminuria

	Microalbuminuria			
Variables	*Absent (n = 62)*	*Present (n = 38)*	*Total (n = 100)*	*p-value*
FBS (mg/dL)				
<100	0 (0%)	0 (0%)	0 (0%)	0.476
100–140	7 (11.3%)	2 (5.3%)	99 (99%)	
>140	55 (88.7%)	36 (94.7%)	91 (91%)	
PPBS (mg/dL)				
<140	0 (0%)	0 (0%)	0 (0%)	0.729
140–200	5 (8.1%)	4 (10.5%)	9 (9%)	
>200	56 (90.3%)	34 (89.5%)	90 (90%)	
HbA1c				
<6	5 (8.1%)	1 (2.6%)	6 (6%)	0.001**
6–9	55 (88.7%)	27 (71.1%)	82 (82%)	
>9	2 (3.2%)	10 (26.3%)	12 (12%)	

**Strongly significant

Table 6: Incidence of retinopathy, neuropathy, and hypertension of patients studied in relation to incidence of microalbuminuria

	Microalbuminuria			
Outcome	*Absent (n = 62)*	*Present (n = 38)*	*Total (n = 100)*	*p-value*
Retinopathy	5 (8.1%)	8 (21.1%)	13 (13%)	0.061^{+}
Neuropathy	18 (29%)	21 (55.3%)	39 (39%)	0.009**
Hypertension	7 (11.3%)	16 (42.1%)	23 (23%)	<0.001**

**Strongly significant; $^{+}$Suggestive significance

patient and duration of diabetes. The clinical markers of generalized endothelial dysfunction manifest in several forms.

Microalbuminuria marks the onset of endothelial dysfunction related to kidney. Since its original description by Mogensen, the estimation of microalbuminuria has been made easy and practical. Microalbuminuria serves as a warning for imminent nephropathy. However, its true value is that it heralds generalized endothelial dysfunction. Thus, diabetic patients with microalbuminuria not only have ongoing progressive nephropathy, but are also likely to have retinopathy. An effort has been made in this study to highlight this issue. Even among randomly selected patients, an incidence of 38% for microalbuminuria is evident. Among various other studies, the prevalence of microalbuminuria ranges from 25 to 35%. A slight increase in the percentage of microalbuminuria in our study can be attributed to several factors, such as large number of elderly patients, longer duration of diabetes, and poor glycemic control.[7-10]

It is very well recognized that microalbuminuria occurs more commonly in diabetic subjects who are more than 50 years of age. In our study, microalbuminuria tended to be 2.54 times more common in the age group of above 50 years as compared with age group less than 50 years. There are many reasons for this phenomenon. Firstly, deterioration in the β-cell function, which occurs pari-passu with increasing duration of diabetes, is likely to contribute to worsening glycemic control. Poor values of HbA1c are known to be associated with increasing incidence of microalbuminuria. In our study, only 1 out of 5 patients who had normal HbA1c (<7.0%) manifested microalbuminuria, whereas with HbA1c values between 6 and 9.0%, 27 out of 55 patients had microalbuminuria, and in patients with HbA1c >9.0%, 2 out of 10 patients had microalbuminuria. It is seen from the above results that even small increments of HbA1c of more than 6.0% result in almost doubling of the incidence of microalbuminuria.

Although this is a cross-sectional study, these findings raise concern regarding the blatant association between poor glycemic control and microalbuminuria in a rural setting.

This study has also brought out a significant association of microalbuminuria with BMI of more than 25 kg/m^2. Of the 22 patients with BMI more than 25, 13 had microalbuminuria (52%). Similar findings have been brought forth by other studies. The possible explanation for this could be[8-10]:

- Increasing BMI is a reflection of insulin resistance, which, in turn, leads to endothelial dysfunction and microalbuminuria.
- Associated hypertension may also be responsible for microalbuminuria.
- Poor glycemic control, which, in turn, is an outcome of insulin resistance, is also held responsible.

Our study has also brought out the correlation between lipid parameters and microalbuminuria. Although no relation could be found between microalbuminuria and hypertriglyceridemia and hypercholesterolemia, the incidence of microalbuminuria is 1.93 times more likely for patients who present with high-density lipoporotein (HDL) values less than 35 mg/dL. A similar

Table 7: Comparison of clinical features of patients studied in relation to incidence of microalbuminuria

	Microalbuminuria			
Variables	*Absent*	*Present*	*Total*	*p-value*
Age in years	50.26 ± 9.90	57.76 ± 11.54	53.11 ± 11.12	0.001**
BMI (kg/m^2)	22.75 ± 3.00	24.54 ± 3.99	23.43 ± 3.50	0.012*
FBS (mg/dL)	172.39 ± 26.22	194.45 ± 34.40	180.77 ± 31.33	<0.001**
PPBS (mg/dL)	244.97 ± 30.20	273.92 ± 48.49	255.97 ± 40.50	<0.001**
HbA1c	7.06 ± 0.81	8.06 ± 1.42	7.44 ± 1.18	<0.001**

**Strongly significant

inverse relationship between HDL and microalbuminuria has been described in many studies.

The incidence of microalbuminuria is significantly associated with the presence of retinopathy (p = 0.061), peripheral neuropathy (p = 0.009), hypertension (p ≤ 0.001), and BMI (p = 0.109) more than 25 kg/m^2. Peripheral neuropathy and hypertension have the neuropathy dependent on similar risk factors. It is also very well known that retinopathy and microalbuminuria have a high concordance rate.

Prevalence of Complications

Complications (%)	Hoorn study[11]	Weersuriya et al[12]	Drivsholm et al[13]		Present study
			M	F	
Diabetic retinopathy	1.9	15.2	5.4	4	21
Diabetic nephropathy	26.7	29	48.1	37.4	18
Diabetic neuropathy	48.3	25.2	19.1	19.1	55

CONCLUSION

The occurrence of microalbuminuria is estimated to be 38% in this study. Microalbuminuria shows a direct relationship with increasing age of patients and increasing duration of diabetes since diagnosis.

A HbA1c value above 7% is associated with 50% or higher occurrence of microalbuminuria.

Patients with a BMI of more than 25 kg/m^2 have significant increase in microalbuminuria.

Occurrence of microalbuminuria is significantly associated with presence of hypertension, neuropathy, retinopathy, and high BMI.

Microalbuminuria is inversely associated with HDL.

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