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ORIGINAL ARTICLE

A STUDY OF MICROALBUMINURIA IN TYPE II DIABETES MELLITUS

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ABSTRACT

Background and Objectives: Diabetic nephropathy is a dreaded complication of Type 2 diabetes mellitus. However in the early stages also known as incipient nephropathy it can be detected by the presence of microalbuminuria. The aim of our study was to know the occurrence of microalbuminuria in patients with Type 2 diabetes mellitus and to note its associations with the duration of diabetes since diagnosis and also the various macrovascular and microvascular complications of diabetes mellitus.Methods. A total of fifty randomly selected diabetic patients satisfying the inclusion criteria were selected for the study. All patients were evaluated in detail along with the testing for microalbuminuria with dipsticks (Micral)Results: 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. An HbA1c 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 significant increase in the incidence of microalbuminuria (p=0.027). The incidence of microalbuminuria is significantly associated with the presence of retinopathy (p=0.073), peripheral neuropathy (p=0.009), ischemic heart disease (p=0.011) and hypertension (p=0.001). Microalbuminuria is inversely associated with HDL (p= 0.089).Interpretation & Conclusion: The occurrence of microalbuminuria in Type 2 diabetic patients of chidambaram was quite high. During the evaluation of diabetic patients the possibility of microalbuminuria and its correlation with various complications of diabetes mellitus should be kept in mind

Keywords: Blood pressure, high sensitivity C-reactive protein, ischemic stroke, NIHSS

1.INTRODUCTION

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

Diabetic nephropathy occurs in as many as 30% of insulin dependant diabetes mellitus patients and 25% of non-insulin dependent diabetes mellitus 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 use of sensitive assay for urinary albumin. At this stage urine is negative for macro albumin and renal function is normal by standard clinical tests. The presence of microalbuminuria precedes the development of overt diabetic nephropathy by 10 to 15 years. It is at this stage that one can hope to reverse diabetic renal disease or prevent its progression. Therapeutic interventions which reverse microalbuminuria include intensified insulin treatment, dietary protein restriction, and control of hypertension by ACE inhibitors and Beta-blockers.

Microalbuminuria thus is an important warning sign for both the physician and the patient which if ignored can lead to 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 marker for widespread microvascular damage in a patient of diabetes mellitus

The aim of this study was to study the occurrence of microalbuminuria in patients with non-insulin dependant diabetes mellitus and also to find out it its association with

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the duration of diabetes mellitus and the microvascular complications and macrovascular complications of diabetes mellitus.

OBJECTIVES

 To study the occurrence of microalbuminuria in patients with type 2 diabetes mellitus attending the rajah muthiah medical college,annamalai university,chidambaram
To note its association with the duration of diabetes and the microvascular and macrovascular complications of diabetes mellitus

2.MATERIALS AND METHODS

Fifty patients of diabetes (NIDDM) admitted to rajah muthiah medical college ,Chidambaram 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 WHO (2) criteria for diagnosis of diabetes mellitus which is : -

1) Symptoms of diabetes mellitus plus a random glucose concentration >200 (11.1mmol/l). The classic symptoms of diabetes mellitus include polyuria, polydipsia and unexplained weight loss

OR

2) Fasting blood glucose >126 mg/dl (7.0mmol/l). Fasting is defined as no caloric intake for at least 8 hours

OR

3) 2 hour post prandial glucose > 200mg/dl (11.1 mmol/l). Among diabetics, the above criteria were considered to include the patients for the study.

Inclusion criteria for case selection:

1) Urine sugar – positive

2) Fasting blood sugar > 126 mg/dl

Exclusion criteria for case selection:

1) Patients with macroalbuminuria

2) Patients with congestive cardiac failure, urinary tract infection.

3) Ketonuria

4) Pregnant patients

5) Patients with overt diabetic nephropathy

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

 Patient's characteristics age, sex, age of onset and duration of diabetes.

 All details regarding the presenting 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 were noted.

A complete clinical examination was carried out in each patient with particular reference to the complications of diabetes like retinopathy, neuropathy, diabetic foot and ischemic heart disease. Height and weight were measured in all cases and body mass index (BMI) was calculated by weight in kg / height in m2

Hypertension was said to be present when there was a history of hypertension or the systolic blood pressure was recorded greater than 160mm of hg and/or diastolic pressure greater than 90 mm of hg on 3 consecutive occasions. Ischemic heart disease was recorded to be present in the presence of suggestive history of angina or myocardial infarction with electrocardiographic evidence. Peripheral neuropathy was judged to be present if there was historical evidence of neuropathic pain, numbness or tingling sensation in the extremities and or absence of ankle jerks along with diminished vibratory threshold or pin prick 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.

Peripheral vascular disease was considered to be present with history of amputations and /or absent of one or more peripheral pulses and /or presence of gangrenous foot.

The following investigations were done in all the patients.

 Microalbuminuria was estimated by Micral test in all the cases.

 Fasting Blood sugar and Postprandial blood sugar

 Glycosylated hemoglobin

 Blood urea and serum creatinine

 Fasting lipid profile

 Urine routine and culture

 Electrocardiogram

 Ultrasonography of the abdomen, echocardiogram and chest x-ray were done in selected cases only.

Estimation of Microalbuminuria by Micral test: All patients having overt macroalbuminuria detected by albustic were excluded from study. Micral test, a immunological rapid dip stick semi qualitative technique for detection of microalbuminuria, was used for estimation of microalbuminuria.

Micral test components: 1 test strip contains monoclonal antibodies against human albumin (immunoglobulin G) labeled with colloid gold 2.2mg, fixed albumin 7.7 mg

TEST PRINCIPLE:

There is a serial arrangement of several reagent pads, which are in fluid communication by a reaction controlling chromatographic process. This step combines one step handling with a complex chemistry. The single reaction steps are as follows:

 Urine of the sample is transported through the wick fleece to the buffer fleece, where acidic urine is adjusted to proper pH. Upon entering the conjugate fleece the antigen – antibody reaction takes place Albumin of the sample is specifically bound to a soluble conjugate of antibodies and marker enzyme resulting in an antigen – conjugate complex

 The excess antibodies are bound to immobilized albumin on the capture matrix and removed from the sample in this way.

 Only the complex of conjugate with sample-albumin reaches the substrate pad. Here the color reaction takes place, the marker enzyme B-Galactosidase cleaves off the purple dye chlorophenol red from the Yellow substrate (chlorophenol red galactoside) in a kinetic reaction. The intensity of the color produced is proportional to the albumin concentration in the urine.

SPECIMEN COLLECTION:

All patients were afebrile during the course of collection of urine and were kept at rest during the collection of urine.

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.

First morning mid stream urine sample that was collected in a sterile container was used for determining microalbuminuria. Test strip was immersed in urine such that fluid level was between the two black bars provided on the strips. Strip was withdrawn after 5 seconds. Strip was placed horizontally across the urine vessel and color change in the test zone was compared with color scale after one minute. Sensitivity of the kit is 0.4ng/ml and measuring range is 0.8 to 10ng/ml.

Microalbuminuria was graded as follows:
Mild (20-50mg/L)- +
Moderate (50-100mg/L) - ++
Severe (100-300mg/L)- +++
Depending on the color change in the strip.

Severity of diabetes was graded based on the HbA1c 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.

Statistical methods75, 76

Chi-square and Fisher Exact test have been used to find the significance of proportion of incidence of microalbuminuria between various levels of study parameters namely BMI, Age, Duration of DM, GHB %, abnormal lipid profile and complications etc. The Odds ratio has been used to find the strength of relationship between the incidence of microalbuminuria and other study parameters. Student t test has been used to find the significance of mean levels of lab parameters between the presence and absence of microalbuminuria

Statistical software: The Statistical software namely SPSS 11.0 and Systat 8.0 were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc.

3.RESULTS AND ANALAYIS STUDY DESIGN

A Prospective clinical study consisting of 50 Type 2 DM patients is undertaken to investigate the pattern and magnitude of microalbuminuria and its relationship with microvascular and macrovascular complications of Type 2 DM.

Table 1: Age and sex distribution

Age in years	Male (n=31)		Female (n=19		Total
	No	%	No	%	No
30-40	2	6.5	2	10.5	4
41-50	9	29.0	5	26.3	14
51-60	8	25.8	6	31.6	14
61-70	9	29.0	4	21.1	13
>70	3	9.7	2	10.5	5
Total	31	100.00	19	100.00	50
Mean age SD	56.68±9.572		56.42±12.522		56.58±10.664
P value	Mean age between male and female = 0.842 Mean age of detection of diabetes = 0.992				

4 patients were in the age group between 30 and 40 years, among whom 2 were male and 2 female patients. 14 patients were in the age group between 41 and 50 years, among whom 9 were male and 5 female patients. 14 patients were in the age group between 51 and 60 years, among whom 8 were male and 6 female patients. 13 patients were in the age group between 61 and 70 years, among whom 9 were male and 4 female patients. 5 patients were in the age group greater than 70 years, among whom 3 were male and 2 female patients. The mean age of male patients in the study was 56.68+9.572 years and that of the female patients was 56.42±12.522 years. The mean age of detection of diabetes mellitus among the male patients was 50.42±7.766 years and in the female patients was 50.16±9.957 years.

The mean age between male and female is not statistically significant with P=0.842 and the mean age of detection of DM is not statistically significant with P=0.992.

Table 2 : Duration of diabetes mellitus since diagnosis

Duration of DM	Male (n=31)		Female (n=19		Total
	No	%	No	%	No
<5.0	19	61.3	11	57.9	30
5.1-10.0	7	22.6	4	21.1	11
10.1-15.0	2	6.5	2	10.5	4
>15.0	3	9.7	2	10.5	5
Total	31	100.00	19	100.00	50
Mean age SD	56.68±9.572		56.42±12.522		56.58± 10.664
P value	0.934				

A total of 30 patients had duration of diabetes since diagnosis less than 5 years among which 19 were male and 11 were female. 11 patients had duration of diabetes since diagnosis between 5 years and 10 years which 7 were male and 4 were female patients. 4 patients had duration of diabetes since diagnosis between 10 years and 15 years among which 2 were male and 2 were female patients. 5 patients had duration of diabetes since diagnosis greater than 15 years among which 3 were male and 2 were female patients. The mean duration of diabetes since diagnosis was 7.52±3.82 years among the male patients and 7.21±4.21 years among the female patients. The mean duration of DM is not statistically significant between male and female patients with P=0.934.

Table 3 : Association of HbAlc with the incidence of Microalbuminuria

HbAlc (n=50)	Microalbuminuria				Total
	-	+	++	+++	
<6.5	5	0	1	0	6
6.5-7.0	5	1	2	0	8
7.0-7.5	10	1	0	0	11
>7.5	12	3	5	5	25
Total	32	5	8	5	50
P value	7.0%, P - 0.024 7.5%, P = 0.001				

6 patients had HbAlc values less than 6.5% and among them 1 were positive for microalbuminuria. 8 patients has HbAlc values between 6.5% and 7.0%, among them 3 were positive for microalbuminuria. 11 patients had HbAlc values between

7.0% and 7.5%, among them 1 were positive for microalbuminuria. 25 patients had a HbA1c values more than 7.5%, among them 13 were positive for microalbuminuria.

Table 4 : Association of body mass index with the incidence of Microalbuminuria

Body mass index (Kg/m^2) (n=50)	Microalbuminuria				Total	OR
	-	+	++	+++		
<19	3	0	1	1	5	0.72 (P=0.614)
19-25	23	1	6	4	34	0.39 (P=0.68[a])
>25	6	4	1	0	11	3.26 (P=0.031*)
Total	32	5	8	5	50	
P Value	P< 0.05					

a Near significance * Significant at 5%
** Significant at 1%

5 patients had a BMI less than $19kg/m^2$ and out of them 2 patients were positive for microalbuminuria. 34 patients had a BMI between $19kg/m^2$ and $25kg/m^2$ out of them 11 patients were positive for microalbuminuria. 11 patients had a BMI above $25kg/m^2$ out of them 5 patients were positive for microalbuminuria.

Incidence of Microalbuminuria is significantly associated & Positively with BMI >25 kg/m^2 and Negatively associated with BMI <25 kg/m^2 with P<0.05.

Table 5 : Association of Lipid Parameters with the incidence of Microalbuminuria

Lipid parameters (n=50)	Microalbuminuria				Total	OR
	-	+	++	+++		
T. Cholesterol (>200 mg/dl)	12	2	1	2	17	1:0.72 (P=0.335)
Triglycerides (> 160 mg/dl)	15	4	5	2	26	1:1.82 (P=0.548)
LDL (>150 mg/dl)	3	2	2	4	11	1:1.62 (P=0.842)
HDL (<30 mg/dl)	12	4	5	3	24	1:1.97 (P=0.124)

a Near significance * Significant at 5%
** Significant at 1%

17 patients had Total cholesterol greater than 200 mg/dl and among them 5 patients were positive for microalbuminuria. 26 patients had Triglycerides greater than 160 mg/dl and among them 11 patients were positive for microalbuminuria. 11 patients had LDL greater than 150 mg/dl and among them 8 patients were positive for microalbuminuria. 24 patients had HDL less than 30 mg/dl and among them 12 patients were positive for microalbuminuria.

Incidence of Microalbuminuria is not significantly associated with the abnormal lipid parameters, however, the incidence of microalbuminuria is 1.97 time more likely for the patients presented with HDL <30 mg/dl.

4.DISCUSSION

Type 2 diabetes mellitus is being increasingly recognized as a disease, which is characterised 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 patient and duration of the diabetes. The clinical markers of the generalized endothelial dysfunction becomes manifest in several forms. Microalbuminuria marks the onset of endothelial dysfunction related to the kidney. Since its original description by Mogensen, the estimation of microalbuminuria is made easy and practical. Microalbuminuria serves as a warning for imminent nephropathy. But its true value is that it heralds generalized endothelial dysfunction. Thus diabetic subjects with microalbuminuria not only have ongoing progressive nephropathy but are also likely to have retinopathy, nephropathy and cardiovascular problems including coronary artery disease and hypertension. 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% 1,2,3,4. 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.

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 to the age group of less than 50 years. There are many reasons for this phenomenon. Firstly deterioration in the b-cell function, which occurs parripassu 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 11 out of 44 patients who had a normal HbA1c (< 7.0%) manifested microalbuminuria, whereas with HbA1c values more than 7, 27 out of 56 (nearly 50%) had microalbuminuria. It is seen from the above result that even small increments of HbA1c more than 7.0% result in almost doubling of the incidence of microalbuminuria.

It is also interesting to note that when HbA1c rises above 7.0%, 22 out of 27 patients tended to have more than 50mg/l and 7 out of 27 had microalbuminuria touching 300mg/l.

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 body mass index of more than 25kg/m2. Of the 22 patients with BMI of more than 25, 13 had microalbuminuria (52%). Similar findings have been brought forth by other studies2, 3, 4. The possible explanation for this could be

- Increasing body mass index is a reflection of insulin resistance which inturn leads to endothelial dysfunction and microalbuminuria.
- Associated hypertension may also be responsible for microalbuminuria.

- Poor glycemic control which inturn 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 correlation could be found between microalbuminuria and hypertriglyceridemia and hypercholesterolemia, the incidence of microalbuminuria is times more likely for the patients who present with HDL values of less than 30mg/dl. A similar inverse relationship between HDL and microalbuminuria has been described in many studies. 5, 1, 2, 4, 6, 7.

The incidence of microalbuminuria is significantly associated with the presence of retinopathy (p=0.073), peripheral neuropathy (p=0.009), ischemic heart disease (p=0.011), hypertension (p=0.001) and body mass index (p=0.027) more than 25kg/m2. Peripheral neuropathy and hypertension have the most significant association with microalbuminuria. This association is not surprising since both hypertension and neuropathy are dependent on similar risk factors. It is also well known that retinopathy and microalbuminuria have a high concordance rate. Several studies have highlighted the occurrence of microalbuminuria as a marker of ischemic heart disease 1, 4, 7. Our study also underscores this point. Out of the total 38 patients with microalbuminuria, 13 of them had ischemic hart disease.

5.SUMMARY

- We studied 50 NIDDM patients for detection of microalbuminuria through the dipstick method.
- The incidence 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 mellitus since diagnosis.
- A HbA1c value above 7% is associated with 50% or higher incidence of microalbuminuria.
- Patients with a body mass index of more than 25kg/m2 have significant increase in the incidence of microalbuminuria.
- Incidence of microalbuminuria is significantly associated with presence of hypertension, neuropathy, Ischemic heart disease, retinopathy and high body mass index.
- Microalbuminuria is inversely associated with HDL.

6.CONCLUSIONS

- The incidence 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 mellitus since diagnosis.
- A HbA1c value above 7% is associated with 50% or higher incidence of microalbuminuria.
- Patients with a body mass index of more than 25kg/m2 have significant increase in the incidence of microalbuminuria.
- Incidence of microalbuminuria is significantly associated with presence of hypertension, neuropathy, Ischemic heart disease, retinopathy and high body mass index.
- Microalbuminuria is inversely associated with HDL.

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