

Prevalence of Microalbuminuria in Type 2 Diabetic Patients in Karachi: Pakistan A Multi-center Study

Muhammad Yakoob Ahmedani, Muhammad Zafar Iqbal Hydrie, Azhar Iqbal, Asma Gul, Waheed Baig Mirza, Abdul Basit Baqai Institute of Diabetology and Endocrinology, Baqai Medical University, Karachi, Pakistan.

Abstract

Objective: To determine the frequency of microalbuminuria and its associations in type-2 diabetic subjects attending diabetes centers/clinics across Karachi, Pakistan.

Methods: Two thousand one hundred subjects with type-2 diabetes were screened for microalbuminuria using Micral test strip II. A single screening test was performed in 25 diabetes centers/units in different districts of Karachi from January 2003 to December 2003.

Results: The overall prevalence of microalbuminuria was 34%. Mean age of subjects was 53.1 years \pm 11.9 years, mean BMI was 25.8 \pm 4.1 and mean duration of diabetes was 8.8 \pm 5.21 years. Fifty seven percent were males and 43% females. Sixty two percent of the subjects had a systolic blood pressure \geq 130 mmHg. Forty five percent had a family history of diabetes and 5% had a family history of hypertension. Univariate analyses demonstrated significant associations between microalbuminuria and age, duration of diabetes, male gender, smoking status, microvascular and macrovascular complications, hypertension, high triglycerides, high serum LDL, low serum HDL, and high fasting & random blood sugars. When adjusted for the effects of other variables in the model, age, diastolic blood pressure, serum LDL and retinopathy were found to be significantly associated with microalbuminuria.

Conclusion: The prevalence of microalbuminuria in type 2 diabetic subjects in this cross-sectional multicentre study across Karachi was 34% and this was significantly related to age, diastolic blood pressure, serum LDL and retinopathy (JPMA 55:382;2005).

Introduction

Diabetic nephropathy is characterized by proteinuria and is the leading cause of end-stage renal disease world wide. It constitutes the major work load of dialysis centers. The estimated cost for dialysis per diabetic subject in Pakistan is around \$30000/year.¹ Diabetic subjects on dialysis and transplant recipients also have higher morbidity and mortality rates than their non diabetic counterparts.² Progression to established diabetic nephropathy occurs through several stages. Microalbuminuria defined as urinary albumin excretion rate of 20-200 μ g/min or urinary protein excretion rate of 30-300 μ g/min predicts future development of overt nephropathy.³ As microalbuminuria can be reversed and the future development of overt diabetic nephropathy significantly reduced, screening for microalbuminuria and timely therapeutic intervention has become standard of care world wide. A cross sectional multi-centered study was conducted in Karachi to establish the frequency of microalbuminuria in Type-2 diabetic subjects.

Patients and Methods

Two thousand one hundred subjects with type-2 diabetes were screened for microalbuminuria on their scheduled visits to the outpatient department of 25 diabetic centers/clinics using a single Micral test strip II test between January 2003 and December 2003.

Known type 2 diabetic subjects more than 18 years of age were included in the study. Subjects were excluded from the study if they came to the clinic after vigorous exercise, had any serious illness such as history of heart failure, Urinary Tract Infections or were known patients of nephropathy.

Clinical details of each subject was recorded in a specified proforma especially designed for this study. This included height, weight and body mass index. Type-2 diabetes was diagnosed based on the WHO study group report criteria.

Subjects were identified as hypertensive if they were on antihypertensive medication or if they had a systolic blood pressure more than 130mmHg or diastolic blood pressure more than 85 mmHg.

A subject was labeled as smoker if he/she was smoking actively or was an active smoker in the last 6 months.

The fundus was examined using Vista 20 direct ophthalmoscope by a diabetologist. The retinopathy was taken as positive if there was evidence of either microdots, hard exudates, soft exudates, new vessels or maculopathy.

Peripheral neuropathy was defined as absent touch or vibratory sensations of the feet. Touch was assessed by 10 gm monofilament and vibration sensation by 128 Hz tuning fork.

Ischemic heart disease was considered to be present if there is history of exertional chest pain, with unequivocal T wave changes in the ECG or if there was a typical history of chest pain documented by previous hospitalization records with ECG changes suggestive of myocardial infarction.

Subjects with absent dorsalis pedis or posterior tibial pulses with or without history of intermittent claudication were taken as having peripheral vascular disease (P.V.D.).

Fasting lipid profile, HbA1c, serum creatinine and urine D/R if done within 6 months of starting the study were noted in the proforma.

Microalbuminuria was defined as a urinary albumin >50 mg/l. Microalbuminuria was checked by using semi-quantitative dry immuno chemical screening strips. (Micral II® test strips) (Roche diagnostic GmbH Mannheim Germany).

Statistical Methods

Descriptive statistics were compared for continuous variables, and percentages for categorical variables. Association between outcome variable and independent variables were sought using chi-square test. To observe the individual effects of each exposure variable, potential confounders were simultaneously controlled by means of multiple logistic regression and ORs with 95% CIs were computed.

Results

The baseline characteristics of the subjects are summarized in Table 1. Mean age of subjects was 53.1 years \pm 11.9 years. Mean Body Mass Index (BMI) was 25.79 \pm 4.05 kg/m². The mean duration of diabetes was 8.8 \pm 5.21 years. Fifty seven percent of the subjects were males while 43% were females, 62% of the subjects had systolic blood pressure more than 130 mmHg. Forty five percent subjects had a family history of diabetes while 5% had a family history of hypertension.

In our study we found that microalbuminuria was more frequent in males (37.1% vs. 29.9%) as compared to females.

Univariate analyses of the factors associated with microalbuminuria are summarized in Table 2. Strong associations were found for microalbuminuria with age, duration of diabetes, male gender, smoking status, microvascular complications including retinopathy, macrovascular complications, hypertension, dyslipidemia, HbA1c, fasting and random blood glucose. The microalbuminuria positive group was older and had a longer duration of diabetes compared to the microalbuminuria negative group ($p < 0.001$). The microalbuminuria positive group had a higher BMI as compared to the microalbuminuria negative group ($p < 0.001$).

Table 1. Baseline characteristics of patients.

Variables	n (%)
Gender (n=2186)	
Male	1237 (56.6)
Female	949 (43.4)
Smoking Status (n=1277)	
Yes	377 (29.5)
No	900 (70.5)
Family history of diabetes	
Yes	981 (44.6)
No	1220 (55.4)
Family history of hypertension	
Yes	110 (5.0)
No	2091 (95.0)
Family history of chronic diseases	
Yes	13 (0.6)
No	2188 (99.4)
Family history of renal diseases	
Yes	7 (0.3)
No	2194 (99.7)
Hypertension (n=1226)	
Yes	685 (55.9)
No	541 (44.1)
Systolic Blood Pressure (n=1101)	
<130	416 (37.8)
>130	685 (62.2)
Diastolic Blood Pressure (n=1100)	
<85	527 (47.9)
>85	573 (52.1)
*Age (in years)	53.10 \pm 11.90
*Duration of diabetes (in years)	8.88 \pm 5.21
*BMI	25.79 \pm 4.05

The microalbuminuria positive group had a higher systolic and diastolic pressure compared to the microalbuminuria negative group ($p < 0.001$). The microalbuminuria positive group had a more deranged lipid profile with higher serum total cholesterol, triglycerides, LDL cholesterol and lower HDL levels compared to the microalbuminuria negative group.

When adjusted for the effects of other variables in the model, age was found to be significantly associated with microalbuminuria. (AOR: 9.67; 95% CI: 4.16 - 22.49).

High diastolic blood pressure was also significantly associated with microalbuminuria (AOR: for DBP > 90 mmHg: 14.42, 95% CI: 3.79-54.75).

Serum LDL was significantly associated with microalbuminuria. The odds of subjects having serum LDL \geq 100 mg/dl among the microalbuminuria group was 8.41 times the odds of serum LDL \geq 100 mg/dl among subjects who did not have microalbuminuria (AOR: 9.19, 95% CI: 2.88-29.37).

Finally, the odds of subjects having retinopathy among the microalbuminuria group was 5.92 times greater than subjects who did not have microalbuminuria (AOR: 5.92, 95% CI: 1.88 -18.69). The goodness of fit test demonstrated good fit ($p = 0.485$).

Discussion

Diabetic nephropathy is the most frequent cause of end stage renal disease. Microalbuminuria is the first clinical detectable sign of involvement of the kidney. It affects

Table 2. Unadjusted and adjusted odds ratio for microalbuminuria in patients.

Variables	Microalbuminuria Absent n (%)	Microalbuminuria Present n (%)	Unadjusted Or for Microalbuminuria (95% CI)	*Adjusted OR for Microalbuminuria (95% CI)
Age >50 yrs (n=1396)	826 (59.5)	570 (78.0)	2.41 (1.97 - 2.96)	10.50 (4.59 - 24.16)
Male	778 (53.9)	459 (61.8)	1.38 (1.15 - 1.65)	†NS
Duration of diabetes (n=1320)				
1-5 years	265 (37.3)	96 (15.8)		NS
6-8 years	201 (28.3)	144 (23.6)	1.98 (1.44 - 2.71)	
9-11 years	140 (19.7)	165 (27.1)	3.25 (2.35 - 4.50)	
>11 years	105 (14.8)	204 (33.5)	5.36 (3.85 - 7.47)	
Smoker	167 (23.4)	210 (35.6)	1.72 (1.35 - 2.19)	NS
Retinopathy (n=1246)	192 (29.2)	284 (48.3)	2.27 (1.80 - 2.86)	6.39 (2.04 - 19.96)
Neuropathy (n=1184)	215 (33.2)	262 (48.8)	1.91 (1.51 - 2.42)	NS
Cerebrovascular (n=1168)	92 (14.5)	130 (24.3)	1.89 (1.40 - 2.54)	NS
Coronary vessels (n=1127)	131 (21.8)	196 (37.3)	2.14 (1.65 - 2.78)	NS
Peripheral Vessels (n=1029)	66 (11.6)	131 (28.4)	3.00 (2.17 - 4.17)	NS
Hypertension	263 (40.6)	422 (73.0)	3.96 (3.11 - 5.04)	NS
Systolic Blood Pressure (mmHg)				NS
<120	203 (34.6)	83 (16.1)		
120<130	99 (16.9)	31 (6.0)	0.77 (0.48 - 1.23)	
130<160	257 (43.8)	316 (61.5)	3.00 (2.22 - 4.08)	
>160	28 (4.8)	84 (16.3)	7.34 (4.46 - 12.08)	
Diastolic Blood Pressure (mmHg)				
<70	231 (39.4)	75 (14.6)		
71-85	168 (28.6)	53 (10.3)	0.97 (0.65 - 1.46)	1.12 (0.31 - 4.01)
85-90	135 (23.0)	235 (45.8)	5.36 (3.83 - 7.50)	6.95 (1.96 - 24.63)
>90	53 (9.0)	150 (29.2)	8.72 (5.8 - 13.10)	14.42 (3.79 - 54.75)
TGL >150 mg/dl	76 (67.3)	192 (93.7)	7.19 (3.62 - 14.29)	NS
HDL < 40 (M) and >50 (F) mg/dl	79 (81.4)	178 (91.3)	2.39 (1.17 - 4.87)	NS
LDL >100 mg/dl	66 (69.5)	178 (93.2)	6.01 (2.95 - 12.27)	9.19 (2.88 - 29.37)
Fasting Blood Sugar >110 mg/dl	341 (93.2)	362 (97.3)	2.65 (1.26 - 5.60)	NS
Random Blood Sugar >200 mg/dl	222 (65.1)	272 (72.3)	1.40 (1.02 - 1.93)	NS
BMI >23	919 (78.7)	558 (86.6)	1.76 (1.34 - 2.29)	NS
*Serum Cholesterol	192.5 ± 41.76	237.44 ± 46.09	1.02 (1.01 - 1.03)	NS
*HBA1c	7.94 ± 1.57	8.18 ± 0.94	1.20 (0.93 - 1.55)	NS

Sample size is different for all variables in univariate analysis. Sample size for final multivariate model was 242. *Mean ±SD is reported.

†Not Significant in final model

BMI - Body Mass Index

between 20-40% of subjects 10-15 years after the onset of diabetes. Once microalbuminuria is present, it progresses over 5-10 years to proteinuria in 20-50% subjects. With microalbuminuria, the decline in renal functions varies but average reduction in glomerular filtration is around 10-12 ml/min/year.⁴ Progression to end stage renal disease is accelerated by hypertension. The process of renal involvement is step wise and microalbuminuria also referred to as incipient nephropathy, is potentially reversible.⁵ Microalbuminuria is also strongly associated with traditional cardiovascular risk factors and cardiovascular complications. Mogensen et al in 1984 reported a significant increase in cardiovascular and total mortality in subjects with type 2 diabetes who had microalbuminuria.⁶ Dineen and Gerstein drew similar conclusions from a meta-analysis of 11 longitudinal studies.⁷ Thus it is important to detect and treat incipient diabetic nephropathy. Screening for microalbuminuria can be performed by four methods: Measurement of albumin to creatinine ratio in random urine sample; 24 hour and timed

overnight urine collection for protein; Microalbuminuria by using micral dip stick. Standard assays to check urinary microalbumin are not generally available in laboratories in Pakistan. An easy and accurate method of detection of microalbuminuria is albumin to creatinine ratio in a spot urine sample. Screening for microalbuminuria with micral II strips is relatively cheap, fast and has an acceptable sensitivity of 96.7% with a specificity of 71%.⁸ All positive tests should be rechecked and confirmed by more specific tests. In our study we did the first initial screening of urine for microalbuminuria excluding causes like exercise, U.T.Is, marked hypertension and hyperglycemia, heart failure, and febrile illness. Micral test II is an optically-read immunoassay specifically for detection of microalbuminuria and the use of these strips has been widely advocated.⁸

Several studies have shown the overall high sensitivity (b/w 79-99%) of Micral strips but lower specificity (67-87%) with higher negative predictive values than positive predictive values.⁴⁻⁹ Due to natural variations in albumin

excretion it is generally recommended to carry out this test 2-3 times to confirm microalbuminuria, hence specificity of the test may not be so crucial as a subsequent test may give a true negative result. Several studies comparing Micral test II and laboratory methods of detecting albuminuria have concluded that it could be used as a screening tool but not as diagnostic tool.

In our study, frequency of microalbuminuria was found to be 34% which is similar to that reported from other Asian countries.¹⁰ Epidemiological studies report prevalence of microalbuminuria in Type 2 diabetes ranging between 8% to 32%.^{11,12} This variation may be due to different criteria used for defining the condition, the stage of the disease, method of assessment and ethnicity.¹³ Microalbuminuria was more frequent in males (37.1% vs. 29.9%) as compared to females which has been observed in other studies.^{14,15} The microalbuminuria positive group was older and had a longer duration of diabetes compared to the microalbuminuria negative group in agreement with other studies.^{14,16} The microalbuminuria positive group had a higher BMI as compared to the microalbuminuria negative group.

A cross-sectional community-based prevalence study with a large sample size of 7841 subjects showed that several CVD risk factors including BMI and W.H.R were associated with urinary albumin excretion. It was shown that obese subjects with central fat distribution had high risk of microalbuminuria independent of blood pressure and plasma glucose. It was also seen that for a given increment in age, BMI and plasma glucose the increment in U.A.E (Urinary albumin excretion) was greater in males than in female subjects.¹⁷ However, a study from Africa showed no relation of microalbuminuria to BMI.¹⁸ There is strong evidence that central obesity is related to insulin resistance.¹⁹ Several studies have shown an association between microalbuminuria and insulin resistance²⁰ and the W.H.O definition of metabolic syndrome lists microalbuminuria as one of the important components of the syndrome.

The microalbuminuria positive group had a higher systolic and diastolic blood pressure compared to the microalbuminuria negative group ($p < 0.001$) which has been observed by others.²¹

The microalbuminuria positive group had a more deranged lipid profile with higher serum total cholesterol, triglycerides, LDL cholesterol and lower HDL compared to the microalbuminuria negative group. Significant lipids abnormalities including high VLDL, LDL and triglycerides and low levels of HDL have also been reported in the literature in subjects with microalbuminuria.²² In a prospective observational study by Gall et al base-line cholesterol was found to be an independent risk factor for the development of microalbuminuria.²³

There were more smokers in the microalbuminuria positive group as compared to the microalbuminuria negative group. Nilsson et al have recently shown an association of smoking with increased HbA1c values and microalbuminuria in diabetic subjects.²⁴

Poor glycaemic control has been shown to be an independent risk factor for microalbuminuria.^{10,24,25} Univariate analysis showed a significant association of microalbuminuria with Fasting Blood Sugars and Random Blood Sugars but not with HbA1c. A possible explanation could be that both microalbuminuria positive and negative groups were on treatment and the mean HbA1c of both the groups was similar; Secondly, glycated hemoglobin is estimated and checked by different methods by different laboratories; hence lack of standardization may be one of the reasons for this finding. Moreover, the last HbA1c values that were available at the time of screening may not be a true representation of overall glycaemic control of that particular individual.

Microalbuminuria positive group also had more microvascular complications like retinopathy and neuropathy than the microalbuminuria negative group. This association of microalbuminuria with retinopathy and neuropathy has been reported by other groups.^{26,27}

Macrovascular disease including coronary, cerebral and peripheral vascular disease was found to be more prevalent in the microalbuminuria positive group similar to the findings in other studies.²⁸

In conclusion the prevalence of microalbuminuria in type 2 diabetes mellitus in this first ever cross-sectional multi-centre study across Karachi is 34%. The risk factors are similar to those reported from other Asian countries. Because of the adverse impact of proteinuria on survival in subjects with type 2 diabetes, screening and intervention programs should be implemented early at the stage of microalbuminuria and risk factors should be treated aggressively.

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