Prevalence and Risk Factors of Microalbuminuria in Nondiabetic Hypertensive Patients

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Abstract

The aim of this study to determine the prevalence of microalbuminuria as well as associated factors in non-diabetic hypertensive patients. Hospital-based cross sectional study. Main outcome of measure is microalbuminuria. A total of 100 nondiabetic hypertensive patients age 18 years without a history of pre-existing kidney disease attending the outpatient department of Community Based Medical College Bangladesh. Mymensingh over a period 6 months from June to December 2014 and who consented and met the criteria were enrolled in this study. A questionnaire including clinical and laboratory data was completed for all cases. The survey data were checked, coded and entered into a SPSS statistical package (Version 11.5). All variables were tested for normal distribution of the data. The data were then cleaned and analyzed using Chi-square (χ^2) Test, One-Way ANOVA statistics and Binary logistic regression model. Results were considered statistically significant for two-sided *P* values of <0.05. The overall prevalence of microalbuminuria was 17% of patients (11(64.7%) were male and 6(35.3%) female). The mean age and BMI were 49.2 ± 9.1 years and 23.5 ± 3.8 kg/m^2 respectively. There were only 2(2%) patients whose systolic BP and diastolic BP were both well controlled (<140/<90 mmHg). while normalization rates of either systolic BP (<140 mmHg) or diastolic BP (<90 mmHg) were 10% and 26% respectively. Age 50 years, low HDL, duration of HTN and triglyceride >150 mg/dl were found independent predictors of elevated UAE with ORs being 0.18, 3.9, 0.13 and 0.49 respectively. Microalbuminuria was not uncommon in non-diabetic hypertensive patients and older age, low HDL, high LDL, raised triglyceride and duration of HTN were significant predictors of microalbuminuria. There is an urgent need to screening of microalbuminuria should be mainstreamed into routine investigation and follow-up of patients with HBP.

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Introduction

Microalbuminuria develops from progressive, subclinical, structural and functional changes within the kidney and represents a sensitive marker of early renal disease[1,2]. Microalbuminuria is typically defined as a 24-h urinary albumin excretion rate (UAE) of 30-300mg (20-200μg/min) or urinary albumin: creatinine ratio (UACR) of 2.5-30mg/mmol in men, 3.5-30mg/mmol in women[3]. The association between renal and cardiovascular (CV) pathologies in advanced kidney and heart disease is well characterised; however, in early disease, these associations are less clearly defined.[4] An early sign of kidney damage, microalbuminuria is a marker of inflammatory process. It is often found in patients with essential hypertension or glucose intolerance. These latter observations suggest that it may be involved in early vascular damage and could be used to predict the onset and progression of CV disease.[1] World Health Organization (WHO) identified microalbuminuria as a component of metabolic syndrome; an indication that microalbuminuria is recognised as a predictor of CV mortality[5,6].

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Microalbuminuria, however, has now been demonstrated to be a sensitive and early predictor of CV risk in patients with hypertension regardless of their diabetic status or whether they have existing renal disease[7,8]. Even very low levels of microalbuminuria are strongly correlated with CV risk[9-12]. The Third Copenhagen City Heart Study-3 assessed the level of microalbuminuria associated with increased risk of coronary heart disease and death in 2762 adults; the data showed that rates of albumin excretion as low as 5µg/min, well below the threshold commonly used to define microalbuminuria, may be associated with an increased risk of CV disease and/or increased CV-related mortality independent of the effect on renal function and hypertension[11]. Clinical studies have shown that small increases in microalbuminuria indicate worsening CV disease, involving endothelial dysfunction and accelerated atherosclerosis and are associated with significant increases in the risk of end-organ damage, major CV events and death[9,10]. In addition, treatment aimed to reduce albuminuria levels have been shown to reduce the risk for cardiovascular events[13] as well as kidney disease progression[14]. In hypertensive subjects, microalbuminuria has now been considered as an essential component in the assessment of subclinical organ damage because its detection is easy and relatively inexpensive[15]. Considering the potential role of micoalbuminuria in predicting subsequent risk levels for cardiovascular and kidney disease complications, the present study was designed to evaluate the prevalence of microalbuminuria and associate risk factors among nondiabetic hypertension patients.

Methods

A hospital-based cross sectional study was conducted in outpatient department of Community Based Medical College Bangladesh. Mymensingh over a period 6 months from June to December 2014. A total of 100 nondiabetic hypertensive patients age 18 years, without a history of pre-existing kidney diseases participated in this study. Patients with previously diagnosed diabetes mellitus or fasting blood glucose 126 mg/dL, impaired kidney function (serum creatinine >1.4 mg/dL in male, or >1.2 mg/dL in female) or history associated with false positive albuminuria (fever, menstruation, urinary tract infection and post exercise) were excluded from the study. Measurements of weight and height were obtained using standardized techniques. The BMI was calculated using the formula: weight (kg)/height (m^2). Blood pressure was recorded in the sitting position in the right arm with a mercury sphygmomanometer. (Diamond Deluxe Industrial Electronics and Products, Pune, India) and rounded off to the nearest 2 mmHg. Two readings were taken 5 min apart and the mean of the two was taken as the final blood pressure reading. A fasting blood sample was taken for estimation of plasma glucose and serum lipids using a Hitachi 912 autoanalyser (Roche Diagnostics, Mannheim, Germany). Microalbumin concentration was measured in a fasting urine sample using an immunoturbidometric assay (Hitachi 902 autoanalyser; Roche Diagnostics). The mean inter and intra-assay coefficients of variation were 3.5 and 4.2%, respectively. A questionnaire including clinical and laboratory data was completed for all cases. The survey data were checked, coded and entered into a SPSS statistical package (Version 11.5). All variables were tested for normal distribution of the data. The data were then cleaned and analyzed using Chi-square (χ^2) Test, One-Way ANOVA statistics and Binary logistic regression model. Results were considered statistically significant for two-sided *P* values of <0.05. Informed consent was taken from the patients in their own language before collecting data.

Results

Most of the patients included in the study were distributed in the age group between 41 – 50 years (44%), male (72%) and educated (77%). In terms of body mass index (BMI), 11% of the patients was under weight, 58% normal and rest 31% over weight and obese. About 30% of the patients had a history of cardiovascular

disease and 11% was habituated in smoking. The mean age and BMI were 49.2 ± 9.1 years and 23.5 ± 3.8 kg/m^2 respectively (Table I).

Table-I: Distribution of patients by demographic characteristics (n = 100)

Demographic characteristics	Frequency	Percentage
Age (years)		
≤40	20	20.0
41 – 50	44	44.0
>50	36	36.0
Gender		
Male	72	72.0
Female	28	28.0
Educational status		
Illiterate	23	230
Primary	16	16.0
SSC	26	26.0
HSC	24	24.0
Graduate & above	11	11.0
BMI (kg/m2)		
< 18.5 (Underweight)	11	11.0
18.5 – 24.9 (Normal)	58	58.0
≥25 (over weight & obese)	31	31.0
Cardiovascular disease	29	29.0
Smoking	11	11.0

The overall prevalence of microalbuminuria was 17% of patients. The gender specific prevalence of micro-albuminuric patients demonstrated that 11(64.7%) were male and remaining 6(35.3%) female (p = 0.759) (Table II).

Table-II: Prevalence of albuminuria according to gender

Gender	Group			
	Normo-albuminuria (n = 75)	Micro-albuminuria (n = 17)	Macro-albuminuria (n = 8)	
Male	55(73.3)	11(64.7)	6(75.0)	0.759
Female	20(26.7)	6(35.3)	2(25.0)	p-value

* Data were analyzed using **Chi-square (c^2) Test.**

Comparision of demographic and clinical characteristics among the study groups shows that the mean age, diastolic BP, serum creatinine, uric acid, total cholesterol and triglyceride were higher in macro-albuminuria group than those in normo-albuminuria and micro-albuminuria groups (57.6 ± 8.8 vs. 46.9 ± 7.7 vs. 55.2 ± 10.1 years; 99 ± 2 vs. 90 ± 7 vs. 92 ± 9 mmHg; 1.6 ± 0.1 vs. 1.2 ± 0.2 vs. 1.3 ± 0.1 mg/dl; 5.9 ± 0.5 vs. 5.8 ± 0.9 vs. 4.9 ± 1.8 mg/dl; 290.7 ± 45.1 vs. 214.7 ± 50.5 vs. 257.1 ± 74.8 mg/dl; 357.2 ± 139.7 vs. 214.2 ± 91.7 vs.189.2 ± 55.1 mg/dl respectively). The mean body mass index, systolic BP, duration of HTN and HDL were found somewhat higher in micro-albuminuria group than normo-albuminuria and macro-albuminuria groups (24.8 ± 4.2 vs. 23.1 ± 3.7 vs. 23.7 ± 3.7 kg/m^2; 157 ± 14 vs. 151 ± 11 vs. 136 ± 3 mmHg; 11.4 ± 8.7 vs. 5.0 ± 2.4 vs. 4.3 ± 2.3 years; 47.7 ± 12.4 vs. 40.8 ± 16.5 vs. 33.6 ± 5.5 mg/dl respectively). However, mean RBS, eGFR and LDL were higher in normo-albuminuria group than micro-albuminuria and macro-albuminuria group (120.8 ± 12.1 vs. 116.3 ± 14.7 vs. 100.0 ± 4.3 mg/dl; 70.4 ± 18.6 vs. 56.9 ± 9.8 vs. 45.7 ± 1.0 ml/min/1.73 m^2 and 125.7 ± 25.6 vs. 116.6 ± 30.5 vs. 120.4 ± 22.6 mg/dl respectively). All the variables except gender, BMI, HDL and LDL were demonstrated to be significantly different among the groups (p < 0.05) (Table III).

Table-III: Comparison of demographic & clinical characteristics among groups

Characteristics	Group			p-value
	Normo-albuminuria (n = 75)	Micro-albuminuria (n = 17)	Macro-albuminuria (n = 8)	
Age (years)#	46.9 ± 7.7	55.2 ± 10.1	57.6 ± 8.8	<0.001
Gender*				
Male	55(73.3)	11(64.7)	6(75.0)	0.759
Female	20(26.7)	6(35.3)	2(25.0)	
BMI (kg/m^2)#	23.1 ± 3.7	24.8 ± 4.2	23.7 ± 3.7	0.288
Systolic BP (mmHg)#	151 ± 11	157 ± 14	136 ± 3	<0.001
Diastolic BP (mmHg)#	90 ± 7	92 ± 9	99 ± 2	0.003
Duration of HTN (months)#	5.0 ± 2.4	11.4 ± 8.7	4.3 ± 2.3	<0.001
RBS (mmol/L)#	120.8 ± 12.1	116.3 ± 14.7	100.0 ± 4.3	<0.001
eGFR (ml/min /1.73 m^2)#	70.4 ± 18.6	56.9 ± 9.8	45.7 ± 1.0	<0.001
Serum creatinine (mg/dl)#	1.2 ± 0.2	1.3 ± 0.1	1.6 ± 0.1	<0.001
Uric acid (mg/dl)#	5.8 ± 0.9	4.9 ± 1.8	5.9 ± 0.5	0.009
Total cholesterol (mg/dl)#	214.7 ± 50.5	257.1 ± 74.8	290.7 ± 45.1	<0.001
Triglyceride (mg/dl)#	214.2 ± 91.7	189.2 ± 55.1	357.2 ± 139.7	<0.001
HDL (mg/dl)#	40.8 ± 16.5	47.7 ± 12.4	33.6 ± 5.5	0.085
LDL (mg/dl)#	125.7 ± 25.6	116.6 ± 30.5	120.4 ± 22.6	0.412

All variables except gender were presented as **mean ± SD.**

 # ANOVA statistics was used to analyses the data; *

Data were analyzed using **Chi-square (c^2) Test.**

Angiotensin converting enzyme-inhibitor (ACE-I) was prescribed in 50% of patients, followed by 0–1 class of drug (49%), angiotensin receptor blocker (32%), ß–blocker (20%), 2 classes of drug (14%), thiazide (12%), NDCCB (7%) and loop diuretics (1%). Patients who were prescribed with ACE-I and 0–1 class of drug have a significantly higher percentage of having micro-albuminuria and macro-albuminuria respectively compared with other classes of drugs (Table IV).

Table-IV. Comparison of antihypertensive medication used among groups

Antihypertensive medication	All (n = 100)	Group			p value
		Normo-albuminuria (n = 75)	Micro-albuminuria (n = 17)	Macro-albuminuria (n = 8)	
ACE-I	50(50.0)	31(41.3)	14(82.4)	5(62.5)	0.007
ARB	32(32.0)	28(37.3)	1(5.9)	3(37.5)	0.040
Thiazide	12(12.0)	12(16.0)	00	00	0.103
NDCCB	7(7.0)	6(8.0)	1(5.9)	00	0.687
Loop diuretics	1(1.0)	1(1.3)	00	00	0.845
ß – blocker	20(20.0)	9(12.0)	9(52.9)	2(25.0)	0.001
On 0–1 class of drug	49(49.0)	42(56.0)	1(5.9)	6(75.0)	<0.001
On 2 classes of drug	14(14.0)	8(10.7)	6(35.3)	00	0.015

* Data were analyzed using **Chi-square (c^2) Test.**

The extent of BP control achieved in study subjects are shown in Table V.

Table-V: Antihypertensive medications used by patients categorized by blood pressure control

Antihypertensive medication	Group			
	<140/ <90 mmHg (n = 2)	≥140/ 90 mmHg (n = 66)	≥140/<90 mmHg (n = 24)	<140/ 90 mmHg (n = 8)
Total (n=100)	**2(2%)**	**66(66%)**	**24(24%)**	**8(8%)**
ACE-I (n=50, 50%)	2(100.0)	32(48.5)	14(58.3)	2(25.0)
ARB (n=32, 32%)	00	21(31.8)	8(33.3)	3(37.5)
Thiazide (n=12,	00	6(9.1)	6(25.0)	00
12%)				
NDCCB (n=7, 7%)	00	7(10.6)	00	00
Loop diuretics (n=1, 1%)	00	1(1.5)	00	00
ß – blocker (n=20, 20%)	2(100.0)	13(19.7)	00	5(62.5)
On 0 – 1 classes of drug (n=49, 49%)	00	34(51.5)	12(50.0)	3(37.5)
On 2 class of drug (n=14, 14%)	00	10(15.2)	4(16.7)	00

There were only 2(2%) patients whose systolic BP and diastolic BP were both well controlled (<140/<90 mmHg), while normalization rates of either systolic BP (<140 mmHg) or diastolic BP (<90 mmHg) were 10% and 26%, respectively. Microalbuminuria and macroalbuminuria were combined and compared with normoalbuminuria group for this analysis. The variables revealed to be significantly associated with elevated urinary albumin excretion (UAE) by univariate analyses were all entered into the model directly. Of the 10 variables, age 50 years, low HDL, duration of HTN and triglyceride >150 mg/dl were found to be the independent predictors of elevated UAE with ORs being 0.18, 3.9, 0.13 and 0.49 respectively (Table VI).

Table-VI: Risk factors of microalbuminuria in nondiabetic hypertensive patients

Variables of interest	Univariate analysis (p-value)	Multivariate analysis	
		dds Ratio (95% CI of OR)	p-value
Age 50 years	<0.001	0.18(0.06 – 0.49)	0.001
Smoking	0.047	0.35(0.10 – 1.26)	0.267
Low HDL (mg/dl)	0.012	3.9(1.29 – 12.02)	0.018
Duration of HTN (months)	<0.001	0.13(0.04 – 0.43)	0.012
Triglyceride >150 mg/dl	0.012	0.49(0.15 – 1.59)	0.048
ACE-I	0.003	0.22(0.08 – 0.62)	0.123
ARB	0.048	3.12(0.97 – 10.04)	0.426
Thiazide	0.033	1.39(1.22 – 1.59)	0.999
ß-blocker	0.001	0.17(0.06 – 0.49)	0.240
On 0 – 1 class of drug	0.015	3.27(1.22 – 8.76)	0.881

Discussion

Various epidemiological and cross sectional studies have reported marked variation in the prevalence of microalbuminuria.[16] Earlier studies on Asian immigrant Indians and native Indians have suggested a high prevalence of microalbuminuria[17-19]. The present study highlights the prevalence of microalbuminuria in hospitalized patient was 17%. This figure differs from those of several previously published reports that indicate a variable but considerably higher prevalence of microalbuminuria[20-30]. These discrepancies are most likely due to different criteria in patient selection (ie, the severity of hypertension, age, coexistence of renal disease and techniques used for the detection of albuminuria).

Therefore, Agewall et al[24] reported an 23% prevalence of microalbuminuria in hypertensive patients. Unfortunately, the study was conducted when patients were receiving antihypertensive drug treatment; therefore, the results of the study were even more difficult to interpret. In the present study, however, great care was taken to exclude patients who were diabetic or had a history or signs of primary renal disease. When necessary, adequate pharmacological washout was performed before urinary albumin excretion was evaluated. Although the strict enforcement of our selection protocol led to the exclusion of patients who did not complete the washout period or did not properly collect urine samples and therefore introduced a potential source of error, it allowed us to screen carefully for comorbid conditions, which might have influenced microalbuminuria. In fact, Damsgaard et al[21] reported a relatively high prevalence of microalbuminuria in a group of 216 elderly hypertensive patients and Summerson et al[29] found a 32% prevalence in a group of black hypertensive subjects, a population known for its susceptibility to developing hypertensive organ damage. Our estimate is almost similar in Thai nondiabetic hypertensive patients with a prevalence of 16.6%. A number of previous studies evaluated the prevalence of microalbuminuria in hypertensive patients has been published, which is varied from 16% in the USA[31]. 11.5% to 30% in Europe[32-36] and 14.4 to 26.2% in Asian populations[37-39]. A significant part of the variability. in the prevalence of microalbuminuria is certainly attributable to different values used to define it, as well as to the techniques and protocols used to evaluate it.

The use of 24-hour urine collection, for example, is likely to yield higher values than overnight collection because of the influence of food and physical activity on urinary albumin excretion. Accordingly, with the use of a 24-hour urine collection procedure, Bigazzi et al[23] reported a high prevalence of microalbuminuria (40%) in a group of 123 hypertensive patients. The measurement of the ACR on first voided morning samples used in the present study was previously shown to be an accurate and reproducible predictor of the AER, perhaps because of the relative stability of renal hemodynamics during night rest. Furthermore, the high day-to-day variability of albumin excretion may have impaired an accurate estimate of persisting microalbuminuria in studies in which only one urinary sample was obtained from each patient[22,26]. In the present study gender specific prevalence of micro-albuminuric patients demonstrated that 11(64.7%) were male and remaining 6(35.3%) female (p = 0.759). Similar findings was observed in earlier studies have reported an increased prevalence of microalbuminuria in men compared with women[40]. Because women have a lower creatinine excretion than men there is, however, a problem about using the albumin creatinine ratio when comparing prevalence across genders. Thus some authors use a lower threshold for men than women[41].

Most of the patients included in the study were distributed in the age group between 41 – 50 years (44%), male (72%) and educated (77%). In terms of body mass index (BMI), 11% of the patients was under weight, 58% normal and rest 31% over weight and obese. About 30% of the patients had a history of cardiovascular disease and 11% was habituated in smoking. These results are in consistent well with the findings of Portuguese patients published by Polonia and associates.[42] Findings of current study also showed that patients who were prescribed with ACE-I and 0 – 1 class of drug have a significantly higher percentage of having micro-albuminuria and macro-albuminuria respectively compared with other classes of drugs. There were only 2(2%) patients whose systolic BP and diastolic BP were both well controlled (<140/<90 mmHg), while normalization rates of either systolic BP (<140 mmHg) or diastolic BP (<90 mmHg) were 10% and 26%, respectively. This was in contrast to other studies report by Gojaseni et al[43] where DCCB have a significantly higher percentage of having microalbuminuria and macroalbuminuria compared with other classes of drugs and a large difference was

observed of patients (47.2%) whose systolic BP and diastolic BP were both well controlled and normalization rates of systolic BP or diastolic BP were 50.8% and 77.6%, respectively.

Microalbuminuria (MA) is a well recognized marker of cardiovascular complications in hypertension, but whether MA can predict adverse outcome in this clinical condition is still a subject for debate. The fact that in hypertensive cohorts those patients who showed an increase in albumin excretion rate also manifested an increased incidence of morbid events indicates that the presence of MA in hypertension may carry an increased cardiovascular risk. However, the prognostic significance of MA remains controversial because no results of prospective studies performed in hypertensive subjects without diabetes mellitus are available. Several factors can affect the prevalence of MA in hypertension, including severity of the disease, selection procedures, concomitant risk factors, degree of obesity, age, duration of hypertension and sex distribution[44]. In the present study, logistic regression analysis revealed age 50 years, low HDL, high LDL, duration of HTN and triglyceride >150 mg/dl as the risk factors for microalbuminuria. The findings most comparable with the present study was one by John et al[45] reported that male sex, older age, longer duration of hypertension and raised blood pressure as risk factors of microalbuminuria, while Vijay et al[46] reported duration of hypertension, 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[45] in a Danish population study[47] and in the Pima Indians.[48] In another study, Palaniappan et al.[49] demonstrated that age, systolic and diastolic blood pressure, stage of hypertension, BMI, waist circumference and obesity were found to be correlating factors with microalbuminuria in both sexes. On the other hand, HDL and triglyceride correlated with microalbuminuria only in women and smoking correlated with microalbuminuria only in men. These observations suggest that urinary excretion of albumin may be a surrogate marker that will useful for the evaluation of individual risk in clinical settings. The findings of others in combination with the findings of this study indicate that many people may benefit from intensive intervention to reduce or normalize the urinary excretion of albumin and whether management of hypertensive populations may be improved by monitoring of albumin excretion rate and whether antihypertensive drugs which are more effective in decreasing urinary albumin can be more beneficial in patients with MA remains to be determined.

Limitations

This is a hospital based cross sectional study. Population based Case control studies should be conducted for assessment of multiple risk factors. This triggers the need for studies with higher sample size to assess various risk factors and mass screening programs.

Conclusion

Microalbuminuria was not uncommon in non-diabetic hypertensive patients. Significant predictors of microalbuminuria included older age, low HDL, high LDL, duration of HTN and raised triglyceride. There is an urgent need to screening of MA should be mainstreamed into routine investigation and follow-up of patients with HBP that could contribute to decreasing the rising prevalence of microalbuminuria.

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