Microalbuminuria in Hypertension: Association with Age, Sex, Body Weight, and Creatinine Clearance

*Islam MN,[1] Hossain MZ,[2] Ferdous A,[3] Islam MN[4]

An observational study was carried out to determined microalbuinuria in 100 albustic negative patient of hypertension with six months or more duration at the Hypertension and Research Center, Rangpur aimed to determine the correlation of microalbuminuria with age, sex, duration of hypertension, BMI, and creatinine clearance in hypertensive Bangladeshi population. Micral test was used for estimation of microalbuminuria. Overall prevalence of microalbuminuria in the present study was 37%. Among the patients with microalbuminuria, 20 were males and 17 were females. Pearson correlation of microalbuminuria with age showed statistically significant linear relationship. Gender-wise correlation analysis of microalbuminuria failed to show any statistical significance. Correlation of microalbuminuria with BMI was also not significant (r = 0.063, p> 0.05). Creatinine clearance negatively correlated with microalbuminuria, but this was statistically insignificant. There was a statistically significant correlation of microalbuminuria with duration of hypertension. Prevalence of microalbuminuria is around 36.6% in hypertension. Incidence of microalbuminuria increases with age as well as with increased duration of hypertension. There is no effect of BMI and sex on the prevalence of microalbuminuria.

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Introduction

Microalbuminuria has a major impact on cardiovascular risk.[1] During the past few years microalbuminuria has become a prognostic marker for cardiovascular disorders. In essential hypertensives, an increased transglomerular passage of albumin may result from several mechanisms - hyperfiltration, glomerular basal membrane abnormalities, endothelial dysfunction and nephrosclerosis.[2] Microalbuminuria which represents albumin excretion of 30 to 300 mg/24 hours or 20- 200 micrograms/minute in timed urine sample[3] or albumin /creatinine ratio 30-299 mg/g creatinine[4] is defined as elevated urinary albumin excretion below the level of clinical albuminuria,[3] undetected by Albustix and can only be detected by special methods such as immunochemical.[5]

Hypertension is one of the most common cardiovascular disorder. The association between microalbuminuria and hypertension was described by Parving et al in 1974.[6]

1. *Dr. Md. Nazrul Islam, Assistant Professor, Department of Biochemistry, Dinajpur Medical College, Dinajpur. nazrulis67@yahoo.com
2. Professor Dr. Md. Zakir Hossain, Professor and Head, Department of Medicine, Rangpur Medical College Hospital
3. Dr. Afsana Ferdous, Assistant Professor, Department of Pharmacology, Rangpur Medical College, Rangpur.
4. Dr. Md. Nurul Islam, Assistant Professor, Department of Biochemistry, ,Dinajpur Medical College, Dinajpur

*For correspondence

Prognostic role of microalbuminuria is possible in early detection and intervention in patients of hypertensive nephropathy like a proved prognostic marker for the development of nephropathy in long standing diabetic patients.[7] Treatment of such patients with drugs like angiotensin converting enzyme inhibitors has been shown to be useful in retarding progress of nephropathy, although the exact mechanism of protection remains to be elucidated.[8] Therefore it is pertinent to detect nephropathy as early as possible to take proper precaution and to initiate appropriate management.

The objective of this study was to detect microalbuminuria in Albustix negative hypertensive patients quantitatively by micral method,[9] an antibody bound enzyme method and study its prevalence, without storing and adding any preservatives to urine as it has been reported that storing of urine sample affects the albumin values depending upon the time and storage conditions.[10] This study was aimed to determine the prevalence of microalbuminuria in hypertensive patients and to evaluate the relation between microalbuminuria and age, sex, duration of hypertension, body mass index, and creatinine clearance.

Methods

This cross-sectional prospective observational study was carried out between June 2013 and July 2014 in the Hypertension and Research Center, Rangpur, to investigate the correlation between microalbuminuria and assumed risk factors. Study was approved by the institutional ethics committee and written informed consent was taken from all the patients. Patients visiting our center were screened for eligibility into the study. Hundred patients with clinically documented systemic hypertension of duration six months or more and negative for albumin in urine by Albustic method were included in the study. Patients with overt albuminuria (>350 mg/day), congestive cardiac failure, urinary tract infection, pregnant patients, patients confined to bed for more than two weeks, and patients on ACE inhibitors for hypertension were excluded from the study. Other causes for microalbuminuria like heavy metal poisoning, connective tissue disorders, and chronic NSAIDs use were also ruled out in the selected patients. The selected patients were studied in detail with history and physical examination, including detailed cardiovascular examination. Body Mass Index (BMI) of all the subjects was calculated by the formula BMI = Weight (Kg) / Height (m^2). Weight and height were recorded by standard instruments. Routine investigations including ,blood glucose, serum creatinine were done by automated analyzer using standard method. Creatinine clearance was calculated based on Cockroft-Gault formula (eCcr).

In the present study, Micral test was used for estimation of microalbuminuria (Roche Diagnostics GmBH, Boehringer Mannheim, Germany). The Micral test is a test-strip method in which the color reaction is mediated by an antibody-bound enzyme.[9,11] This method has shown good correlations with radioimmunoassay and can be readily used for screening. Presence of microalbuminuria in morning spot urine sample was defined as urinary albumin excretion 30-300 mg/L (mg of albumin per liter of urine). All patients were afebrile during the collection of urine. Urine was first tested for albumin by Albustick method (Combur test). Only those patients who were negative for albumin in urine by Albustick method were included in this study. First morning mid-stream urine sample was collected in sterile container. Test strip was immersed in urine such that the fluid level was between two black bars. Strip was withdrawn after five seconds. Strip was

placed horizontally across the urine vessel and the color change in test zone was compared with color scale after one minute. Sensitivity of the kit is 0.4 ng/ml and the measuring range is 0.8–10 ng/ ml. Microalbuminuria was graded as mild (20–50 mg/L), moderate (50–100 mg/L), or severe (100–300 mg/L) depending on the color change in the strip. Test was repeated twice for selecting the patients into the study.

Statistical analysis

Data collected were analyzed by student's '*t*' test or chi-square test as appropriate. Pearson correlation test was used to analyze the correlation of microalbuminuria with independent variables like age, sex, BMI, duration of hypertension, and creatinine clearance. Probability (p) value less than 0.05 was regarded as statistically significant.

Results

A total of 100 patients, 57 males and 43 females, were included in the study. Overall prevalence of microalbuminuria in the present study was 37%. Among the patients with microalbuminuria, 20 (54.05%) were males and 17 (45.95%) were females. Among 37 microalbuminuric patients, 9 patients had mild albuminuria, 18 had moderate albuminuria, and 10 had severe albuminuria. Baseline characteristics of the patients are shown in Table I.

Age of patients at diagnosis ranged between 30–70 years. Mean age at onset of hypertension in microalbuminuric patients was 51.7 ± 9.8 years and in normoalbuminuric patients it was 46 ± 11.6 years. The difference between the two groups was statistically significant. Gender-wise comparisons of baseline characteristics are shown in Table II. There was statistically significant difference in creatinine clearance between males and females. Creatinine clearance was much lesser in females. Pearson correlation of microalbuminuria with age showed significant linear relationship (r = 0.528, P < 0.001, fig-1). Gender-wise correlation analysis of microalbuminuria was not significant (Table III)

Eleven patients had BMI >30 kg/m^2, among them four had microalbuminuria (10.8%) and seven had normoalbuminuric (11.1%). Mean BMI of microalbuminuric patients was 22.3 ± 6.9 kg/m^2 and for normoalbuminuric patients it was 21.6 ± 4.2 kg/m^2. The difference between the groups was not statistically significant. Pearson correlation analysis also did not show any significance for microalbuminuria and BMI (r = 0.063, P > 0.05, fig-2). Creatinine clearance negatively correlated with microalbuminuria, though statistically insignificant (r = −0.158, P > 0.05, fig-3). Maximum number of patients (54) had duration of hypertension between six months and five years (Table IV**)**. Among these, four (7.4%) had microalbuminuria. Twenty four patients had duration of hypertension between five and ten years. Among them 12 (50%) had microalbuminuria. Eleven patients were with duration of hypertension between 10 and 15 years, among them 10 (90%) were positive for microalbuminuria. Remaining eleven patients had duration of hypertension more than 15 years, all of them were positive for microalbuminuria (100%).

Mean duration of hypertension in microalbuminuric patients was 10.7 ± 5.0 years while in normoalbuminuric patients it was 3.2 ± 2.0 years, which was statistically highly significant. Pearson correlation analysis showed statistically significant correlation of microalbuminuria with duration of hypertension (r = 0.839, p < 0.0001 (Table III**)**. Relationship between severity of hypertension and microalbuminuria was significant.

Table I: Baseline characteristics of the patients

Variable	All patients	Range	Microalbuminuric patients (*n* = 37)	Normoalbuminuric patients (*n* 63)	*P* value
Sex (M/F)	57/43		20/17	39/24	
Mean age (years)	54.18 ± 13.73	30–85	62.49 ± 12.14	49.3 ± 12.25	<0.001
Mean age at onset of hypertension (years)	48.6 ± 10.5	28–70	51.7 ± 9.8	46 ± 11.6	<0.001
BMI (kg/m^2)	22.09 ± 4.99	11.6–38.2	22.88 ± 6.06	21.64 ± 4.23	0.23
Serum creatinine (mg/dl)	0.97 ± 0.17	0.6–1.3	0.98 ± 0.16	0.97 ± 0.18	0.61
Creatinine clearance (ml/min/m^2)	80.35 ± 21.81	43–166	75.43 ± 20.57	83.24 ± 22.16	0.08
Duration of hypertension (years)	5.97 ± 4.98	1–20	10.66 ± 5.02	3.21 ± 2.01	<0.001

All values are expressed as mean ± SD; Student's '*t*' test

Table II: Gender-wise comparison of baseline characteristics

Variable	Males (*n* = 59)	Females (*n* = 41)	p
Mean age (years)	62.97 ± 12.95	55.93 ± 14.78	0.29
BMI (kg/m^2)	21.66 ± 4.77	22.73 ± 5.29	0.29
Serum creatinine (mg/dl)	0.97 ± 0.18	0.97 ± 0.17	0.96
Creatinine clearance (ml/min/m^2)	90.37 ± 20.65	65.93 ± 14.06	<0.001
Duration of hypertension (years)	5.68 ± 5.08	6.39 ± 4.86	0.48

All values are expressed as mean ± SD; Student's '*t*' test

Table III: Correlation of microalbuminuria with independent variables

Variables	Mean ± SD	Correlation coefficient (*r*)
Age (years)	54.18 ± 13.73	0.529*
Sex (M/F)	59/61	0.062
BMI (kg/m^2)	22.09 ± 4.99	0.063
Duration of hypertension (years)	5.97 ± 4.98	0.839**
Creatinine clearance (ml/min/m^2)	80.35 ± 21.81	−0.158

Pearson correlation; $^*P < 0.001$, $^{**}P < 0.0001$

Table IV: Prevalence of microalbuminuria in relation to duration of hypertension

Duration of diabetes (years)	No. of microalbuminuric patients (%)	No. of normoalbuminuric patients (%)	Total (*n*)
1-5	4 (7.4)**	50 (92.6)	54
5-10	12 (50)	12 (50)	24
10-15	10 (90.9)*	1 (9.1)	11
>15	11 (100)**	0	11

Chi-square test; $^*P < 0.01$, $^{**}P < 0.001$

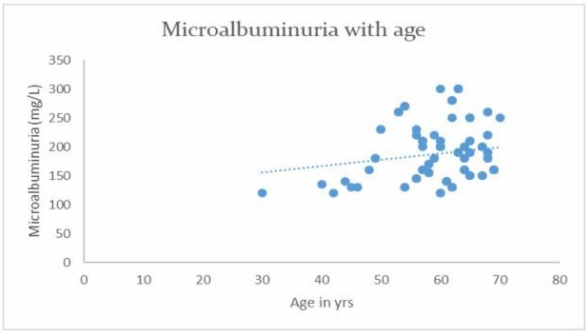

Fig 1. Positive correlation between the severity of microalbuminuria and age

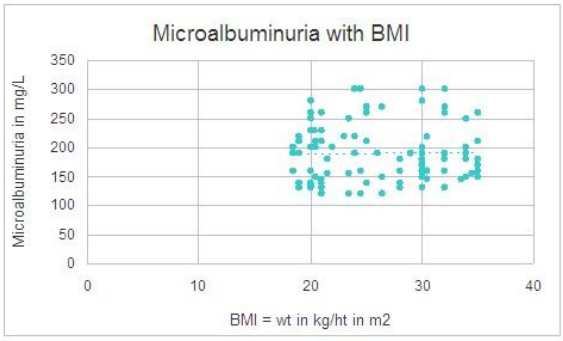

Fig 2: No correlation between the severity of microalbuminuria with BMI

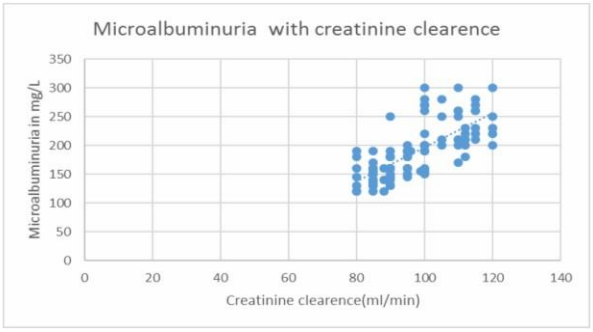

Fig 3: Showing positive correlation between the severities of microalbuminuria with creatinine clearance.

Discussion

This cross-sectional study presents data on prevalence and associations of microalbuminuria with various parameters in hypertension. Present study has shown prevalence of microalbuminuria at 36.6%, which is slightly higher when compared to the study by Parduman *et al*, where prevalence was reported at 33.3%.[12]

The large study on the prevalence of microalbuminuria by Bigazzi et al in 1992 reported the figure of 40% [13,25], while subsequent studies reported the variation from 4.7% to 40%.[14,17]The difference in prevalence's are expected as the differences can also be due to differences in definition of microalbuminuria (i.e. cut off values), method of urine collection (timed versus random), quality of albumin assay, size of study (small cohort versus large population based) and ethnic background of patients. Higher prevalence in the present study may be due to the fact that most of the patients were on irregular treatment and also may be due to the small sample size.

Method of estimation of microalbuminuria as well as ethnical differences would have also played a role in giving higher prevalence in the present study. Irregular treatment due to lack of awareness seems to be the strongest factor influencing transition from normoalbuminuria to microalbuminuria. Present study has shown statistically significant linear relationship of degree of albuminuria with age. Earlier studies have also shown positive correlation of microalbuminuria with age of the patients.[15,16] Our study has not shown gender-wise correlation of microalbuminuria, which is in contrast to the previous studies that have reported male dominance in the prevalence of microalbuminuria.

As reported in many studies, our study failed to show any correlation between BMI and microalbuminuria.[12] This may be due to the confounding variables like duration of hypertension that would have played a major role in the occurrence of microalbuminuria. Even though it is reported that microalbuminuria is more prevalent in obese

hypertensive.[17] This is in contradiction to the study by Redon.[18] where correlation was reported between BMI and albumin excretion. However, Nishijo et al in a study of 245 non diabetic Japanese men concluded that urinary albumin was significantly related to systolic and diastolic blood pressure in a manner independent of other factors such as BMI.[19] Creatinine clearance has shown slight negative correlation with microalbuminuria in the present study, though statistically insignificant. Serum creatinine and creatinine clearance was within normal range in all the patients.

Hypertensive nephropathy can be categorized clinically into different stages with respect to patient's illness condition and laboratory indexes. Hypertensive nephropathy is divided into the 1. Microalbuminuria: abnormal excretion of albumin in urine with normal kidney function and negative urine protein; 2. Clinical proteinuria: positive urine protein, 24-hour urine protein >0.5g with normal renal function; 3. Renal insufficiency: decrease of Ccr and increase of Scr. This stage include non-dialysis and dialysis period: Non-dialysis - Ccr is 80-10ml/min, 133μmol/L; Dialysis (ESRD) - Ccr<10ml/min, Scr>707μmol/L.[20]

Present study has shown positive correlation of microalbuminuria with duration of hypertension which is in accordance with many previous reports. Duration of hypertension has significant contribution for an increased transglomerular passage of albumin may result from several mechanisms hyperfiltration, glomerular basal membrane abnormalities, endothelial dysfunction and nephrosclerosis.[3] Limitations of the present study must also be considered. As our study was not based on the general population, selection bias might have affected the outcome of the study. Larger sample size in general population may be required to confirm the results of the present study.

In conclusion, our study has found higher prevalence of microalbuminuria (36.6%) in hypertension, which is the predictor of later development of diabetic nephropathy. Incidence of microalbuminuria increases with age as well as with increased duration of hypertension. There is no effect of BMI and sex on the prevalence of microalbuminuria in hypertension. Results of our study confirm and extend the previous observations in small selected groups of patients with hypertension. Creatinine clearance will be within normal range in microalbuminuric patients. But the presence of microalbuminuria alerts the physician to prevent further renal damage by timely administration of ACE inhibitors and correction of risk factors. Urinary excretion of albumin should be monitored routinely in patients with hypertension.

This study strongly recommends introduction of "microalbuminuria screening, intervention and education" program. This program should be designed to obtain data of the prevalence of microalbuminuria in hypertensive patients treated in various hospitals, establishing an easy screening program for microalbuminuria, implementation of specific intervention methods and educate the hypertensive patients about the consequences of irregular treatment. Such programs can substantially modify the natural history of renal involvement and possibly reduce the incidence of end stage renal failure in the hypertensive patients.

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