ORIGINAL ARTICLE

Prevalence and Clinical Correlates of Microalbuminuria in Patients with Essential Hypertension - A Tertiary Care Center Cross Sectional Study

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Abstract

Introduction: Albuminuria is predictor of target organ damage and worse cardiovascular outcomes. Microalbuminuria has been found in a large number of patients with essential hypertension. Aim of our study was to evaluate the frequency of microalbuminuria in essential hypertension and to study its correlation with severity of hypertension and target organ damage.

Materials and methods: This cross-sectional study was conducted at the outpatient clinic of General Medicine department of Pt. B D Sharma PGIMS, Rohtak. Hundred patients of essential hypertension (group A) in the age group of 18-65 years were included in the study. A control group (group B) consisting of hundred healthy normotensive, age and sex matched volunteers were also entered into the study. Arterial blood pressure was measured by digital sphygmomanometer after five minutes of rest; the values reported represented the average of three consecutive measurements taken over a 15-minute period. Urine albumin excretion (UAE) was estimated by an immunoturbidometry method. Microalbuminuria was defined as UAE between 30 and 300 mg/24 hours. Statistical analysis was performed by standard methods to measure rates and proportions; chi square test was used for analyzing the associations between the variables.

Result: In this study it was observed that prevalence of microalbuminuria in essential hypertension was 47%. Risk factors for microalbuminuria included higher age, SBP and MAP. Microalbuminuria was associated with dyslipidemia, deranged renal parameters and end organ damage in form of LVH, ischemic changes, hypertensive retinopathy and renal dysfunction. In conclusion, this study confirmed that increased urinary albumin excretion is associated with a worse pattern of cardiovascular risk factors and is a marker of concomitant cardiovascular damage in essential hypertension.

Conclusion: Microalbuminuria can therefore be regarded as a useful, relatively inexpensive, integrated marker to help identify patients at higher cardiovascular risk for whom more aggressive preventive strategies and additional treatment measures may be advisable.

Introduction

Hypertension is a major public health problem worldwide. The incidence of hypertension in India is around 10 % in the adult population.[1] Essential hypertension produces proteinuria and a significant reduction in renal function in 5–15% of patients.[2] Hypertension is also an independent predisposing factor for heart failure, coronary artery disease, stroke and peripheral arterial disease (PAD). Microalbuminuria is defined as urinary albumin excretion 30-300 mg/24 hour or albumin/creatinine ratio 30-300 mg/g.[3] Main mechanisms proposed for the greater urinary albumin excretion (UAE) in patients with essential hypertension include increased glomerular hydrostatic pressure, increased permeability of the glomerular basement membrane and tubular alterations.[4] Although several studies have attempted to define the prevalence of microalbuminuria in essential hypertension, the exact figure is still unclear. The published prevalence of microalbuminuria in hypertensive subjects ranges from 4.7% to 58.4%.[5,6] This wide variability in the incidence of micro-albuminuria in these studies may be related to the severity of hypertension, selection criteria, racial difference and, in some cases, to smaller number of patients studied. The advent of more sensitive methods to quantitate the urinary albumin excretion (UAE) has revealed higher frequency of microalbuminuria in patients with hypertension than in normotensive population. Microalbuminuria is independently associated with ischemic heart disease, heart failure, hyperlipidemia and atherosclerosis. Risk of stroke increases by about 50% for every 10 fold increase in urine albumin excretion. Subjects with microalbuminuria have 90% greater risk for developing future stroke incidents compared with individuals with normoalbuminuria. It is also associated with cerebral small vessel disease, cognitive dysfunction, dementia and Alzheimer disease.

Studies have shown that microalbuminuria is associated with a cluster of metabolic and non-metabolic risk factors which is also a marker of target organ damage

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Table 1: Clinical and laboratory characteristics of study subjects

Parameters	Group A (n=100)	Group B (n=100)	p value
BMI (kg/m^2)	24.03±3.09 (16.8-31.6)	23.53±2.56 (19.3-31.2)	> 0.1
Blood pressure			
SBP (mmHg)	151.24±7.03 (142-172)	121.08±7.17 (104-136)	0.001
DBP (mm Hg)	95.92±3.69 (90-108)	79.40±3.96 (70-86)	0.001
MAP (mmHg)	114.40±4.44	92.98±4.17	0.001
Number of patients			
Stage 1 HT (%)	85 (85%)		
Stage 2 HT (%)	15 (15%)		
Hemoglobin (g/dl)	13.71±1.24 (10.8-16.2)	13.61±1.70 (10-16.4)	> 0.1
FBG (mg/dl)	85.44±5.92 (75-96)	84.54±4.71 (76-94)	> 0.1
Sr. triglycerides (mg/dl)	114.04±23.35 (60-201)	113.56±20.44 (77-167)	> 0.1
Sr. cholesterol (mg/dl)	188.77±17.83 (136-235)	179.21±15.91 (140-216)	< 0.01
Sr. HDL (mg/dl)	43.47±3.63 (36-52)	44.97±4.54 (35-57)	< 0.01
Sr. LDL (mg/dl)	120.78±16.80 (90-167)	118.29±12.79 (76-140)	< 0.01
Sr. VLDL (mg/dl)	25.12±2.69 (19-32)	25.70±3.22 (18-36)	> 0.1
Blood urea (mg/dl)	28.77±6.80 (16-50)	22.22±4.22 (13-32)	< 0.001
Sr. creatinine (mg/dl)	0.85±0.09 (0.7-1.1)	0.78±0.06 (0.6-1.0)	< 0.001
Sr. uric acid (mg/dl)	4.60±0.89 (2.8-6.7)	3.90±0.63 (2.6-5.9)	< 0.001
Sr. sodium (meq/L)	141.18±3.51 (132-149)	141.39±3.24 (132-149)	> 0.1
Sr. potassium (meq/L)	4.19±0.35 (3.2-5.0)	3.93±0.26 (3.3-4.7)	0.001
Serum calcium (meq/L)	9.02±0.25 (8.6-9.7)	9.10±0.28 (8.5-9.8)	> 0.1
Sr. phosphorus (meq/L)	3.75±0.44 (2.9-4.6)	3.34±0.42 (2.5-4.4)	0.001
Sr. protein (g/dl)	7.02±0.32 (6.2-7.7)	7.02±0.37 (6.2-7.7)	> 0.1
Sr. albumin (g/dl)	4.01±0.34 (3.3-5.0)	4.05±0.37 (3.3-5.0)	> 0.1
eGFR (ml/min/1.73m^2)	92.70±12.58 (80.06-127.3)	98.57±11.06 (84.01-123.25)	0.001
UAE (mg/24 hours)	49.88±51.72 (5.2-278.8)	8.76±3.49 (3.3-18.4)	< 0.001
Pts. with microalbuminuria no. (%)	47 (47%)	Nil	

Table 2: Comparison of microalbuminuric and normoalbuminuric hypertensive patients

Parameter	Group X (n=47)	Group Y (n=53)	p value
Age	45.3±10.02	40.28±9.8	< 0.05
BMI	24.23±3.12	23.98±2.99	> 0.1
Smokers (%)	22/47 (46.81%)	19/53 (35.84%)	0.001
Sex			
Male	27	23	> 0.1
Female	20	30	
SBP (mm Hg)	155.32±6.99	147.83±7.2	0.01
DBP (mmHg)	96.23±4.1	94.88±3.6	> 0.1
MAP (mmHg)	117.23±4.18	111.88±2.89	0.01
Fasting blood sugar (mg/dl)	84.97±6.14	83.96±5.73	> 0.1
Serum triglyceride (mg/dl)	121.76±24.51	107.18±20.13	0.001
Serum cholesterol (mg/dl)	199.27±14.30	179.45±15.36	0.001
Serum HDL (mg/dl)	43.61±3.43	43.33±3.82	> 0.1
Serum LDL (mg/dl)	131.23±14.02	111.50±13.31	0.001
Serum VLDL (mg/dl)	25.27±2.88	24.98±2.52	< 0.1
Blood Urea (mg/dl)	27.02±6.22	24.88±5.30	>0.05
Serum creatinine (mg/dl)	0.84±0.06	0.80±0.08	< 0.05
Serum uric acid (mg/dl)	5.29±0.58	4.00±0.65	0.001
Serim sodium (meq/L)	141.02±3.34	141.32±3.67	> 0.1
Serum potassium (meq/L)	4.23±0.35	4.15±0.36	> 0.1
Serum calcium (meq/L)	9.03±0.22	9.10±0.25	> 0.1
Serum phosphorus (meq/L)	3.75±0.41	3.75±0.48	> 0.1
Serum proteins (g/dl)	6.98±0.32	7.08±0.32	> 0.1
Serum albumin (g/dl)	3.99±0.31	4.07±0.36	> 0.1
eGFR (ml/min/1.73m^2)	91.97±9.91	99.01±13.81	0.005
UAE (mg/24 hours)	90.43±50.59	13.91±4.89	0.001
ECG-LVH (%)	15 (31.91%)	9 (16.98%)	0.005
ECG-Ischemic changes (%)	8 (17.02%)	4 (7.54%)	0.005
CXR-cardiomegaly (%)	7 (14.89%)	4 (7.54%)	0.005
Hypertensive retinopathy (%)	20 (42.55%)	13 (24.52%)	0.005

and an independent predictor of cardiovascular morbidity and mortality in patients with essential hypertension.[7] Early screening for microalbuminuria in patients of essential hypertension and thereby early initiation of treatment might help in reducing ongoing target organ damage. With this background the present study was initiated at a tertiary care centre to investigate the prevalence of albumin excretion rate and its relation with essential hypertension.

Material and Methods

This cross-sectional study was conducted at the outpatient clinic of General Medicine department of Pt. B D Sharma PGIMS, Rohtak. Hundred patients of essential hypertension (group A) in the age group of 18-65 years, who recorded a high blood pressure as per JNC 7 criteria and a creatinine clearance greater than 80 ml/min/1.73 m^2 were included in the study. A control group (group B) consisting of hundred healthy normotensive, age and sex matched volunteers were also entered into the study. Informed consent and ethical justification was taken for both the groups. Patients with secondary hypertension were excluded from the study after adequately investigating in an appropriate manner for with regular laboratory analyses. Renal, adrenal and other causes of secondary hypertension were excluded based on findings of urinalysis, serum electrolytes, serum creatinine, creatinine clearance, renal ultrasonography, CT chest and abdomen, and special investigation; if required. Pregnant women, women on birth control pills, patients with diabetes mellitus, urinary tract infection, renal disease, macro albuminuria, patients with doubtful history of hypertension and patients already on drugs affecting urine albumin excretion(UAE) like angiotensin converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, beta blockers were also excluded from study. Blood and urine creatinine were measured using an autoanalyzer. Urine for estimation of microalbuminuria was stored at -20°C. UAE was estimated by an immunoturbidometry method. Microalbuminuria was defined as UAE between 30 and 300 mg/24 hours.[3] Arterial blood pressure was measured using a digital blood pressure monitor (Omron, model no. - HEM 7132) after five minutes of rest; the values reported represented the average of three consecutive measurements taken over a 15-minute period. Mean arterial pressure was calculated by adding diastolic blood pressure with one-third of pulse pressure. So, with this background this study was conducted with aim of evaluating frequency of microalbuminuria in essential hypertension and its association with severity of hypertension and target organ dysfunction.

The data collected during the study was entered in the Microsoft excel format and was analysed using SPSS 20.0 version. Analysis was performed by standard methods for rates and proportions; chi square test, paired t-test, unpaired t-test, one way analysis of variance. A two tail p-value was used

Table 3: Age distribution of microalbuminuric and normoalbuminuric hypertensive subjects

Age group	Microalbuminuric (n=47)	Normoalbuminuric (n=53)	Total (n=100)
18-29 years	4 (28.57%)	10 (71.43%)	14
30-39 years	10 (41.67%)	14 (58.33%)	24
40-49 years	13 (50%)	13 (28.3%)	26
50-59 years	16 (55.17%)	13 (44.83%)	29
≥ 60 years	4 (57.14%)	3 (42.86%)	7

Table 4: Comparison of 24 hours mean albumin excretion between microalbuminuric hypertensive subjects

Parameter		No. of subjects (n=47)	24 hours mean UAE (mg/24hrs)	Chi square test p value
LVH	Yes	24	115.5±36.3	0.005
	No	23	64.3±29.5	
Ischemic changes	Yes	12	137.6±40.2	0.005
	No	35	74.3±27.9	
Hypertensive retinopathy	Yes	33	103.2±29.5	< 0.005
	No	14	57.7±24.4	

for calculating statistical significance. A p value of <0.05 was taken statistically significant.

Result

Mean age was 42.50±10.89 in hypertensive patients (group A) and 41.9±9.55 in control group (group B) (p value >0.05) and rest demographic variables including gender distribution, body mass index and smoking habit were also comparable in both groups. In group A, systolic blood pressure, diastolic blood pressure and mean arterial pressure was significantly higher than control group.Out of 100 hypertensive patients; 85 belonged to stage 1 and rest 15 were stage 2 hypertensive (Table 1).

On comparison of group A and B; blood urea, serum creatinine, serum uric acid were significantly higher in group A (p value <0.001). Serum cholesterol, serum LDL were also significantly higher (p value <0.01) and serum HDL was significantly lower (p value <0.01) in hypertensive group A. In group A; eGFR was significantly less than group B (p value <0.001). 24 hours average urine albumin excretion was also significantly higher in group A (p value <0.001). Out of 100 group A subjects 47 (47%) had microalbuminuria while none of the group B subjects had microalbuminuria (Table 1). 38.82% stage 1 hypertensive patients and 93.33% stage 2 hypertensive patients had microalbuminuria. LVH and ischemic changes (ST depression, T wave inversion and strain pattern) on ECG, cardiomegaly on chest x-ray and hypertensive retinopathic changes were significantly higher in hypertensive group as compared to control group (p value <0.001). In stage 2 hypertensive subjects LVH and ischemic changes were present in 58.33% and 83.33% subjects; respectively as compared to 41.66% and 16.67%; respectively in stage 1 hypertensive patients and the difference was statistically significant (p value <0.001). On chest x-ray, 81.82% stage 2 hypertensive subjects had cardiomegaly as compared to 18.18% stage 1 hypertensive patients (p value <0.001). Similar findings were obtained in relation to hypertensive retinopathy indicating increasing prevalence of hypertensive retinopathy with increasing severity of hypertension.

Subgroup analysis of various parameters between microalbuminuric hypertensive subjects (group X,n-47) and normoalbuminuric hypertensive subjects (group Y, n-53) was done which revealed significant difference in age, smoking habit, systolic blood pressure, mean arterial pressure, serum triglyceride, serum cholesterol, serum LDL, blood urea, serum creatinine and serum uric acid. eGFR was significantly lower in group X as compared to group Y with p value <0.001. 24 hours urine albumin excretion was significantly higher in group X when matched to group Y with p value <0.001. LVH and ischemic changes on ECG, cardiomegaly on chest x-ray and hypertensive retinopathy on fundus examination was significantly higher in group X (Table 2). Age distribution of subjects in group X and Y showed increasing prevalence of microalbuminuria with age (Table 3). Positive correlation was found between severity of hypertension and urine albumin excretion (Pearson's coefficient 0.648). 24 hours mean UAE was significantly higher in group X subjects with ECG changes (LVH and ischemic changes) and hypertensive retinopathy changes (Table 4). 24 hours UAE was found to be positively correlated to serum creatinine (Pearson's coefficient 0.702) and negatively correlated to eGFR (Pearson's coefficient -0.732).

Discussion

Microalbuminuria and vascular dysfunctions are known to occur early in the course of essential hypertension. Microalbuminuria has been postulated to represent the renal manifestation of generalized, genetically conditioned vascular endothelial dysfunction that may underlie the link between an increased UAE and an elevated risk for cardiovascular disease.[3] Endothelial dysfunction has been proposed to be a plausible pathophysiological mechanism of microalbuminuria.[8]

Hypertensive nephropathy is a common finding in patients with hypertension and is a common cause of chronic kidney disease. Progressive nephrosclerosis from vasculo-endothelial disease is the renal correlate of the same process that lead to coronary artery diseases, cerebrovascular diseases, hypertensive retinopathy and left ventricular dysfunction.[9] It has been pointed out that cardiovascular risk progressively increases as renal function declines[10]. Losartan Intervention For Endpoint reduction in hypertension (LIFE) study confirmed the predictive power of microalbuminuria and its changes over time in a large cohort of carefully monitored patients during a five-year follow-up.[11] Some studies have suggested that the presence of microalbuminuria also increases the relative risk of an adverse cardiovascular events like hypercholesterolemia.[12] The conventional methods of detecting renal damage in hypertensive patients, which includes the measurement of blood urea nitrogen, creatinine and proteinuria, are relatively insensitive and only shows abnormalities when the disease process is advanced. Recently there has been considerable interest in the quantitative measurement of albuminuria to detect the subtle effects of hypertension on the kidney. Microalbuminuria has been defined as urine albumin excretion 30- 300 mg/24 hours or urine albumin creatinine ratio 30-300 mg/g. While international therapeutic guidelines recommend that the diagnosis of microalbuminuria should be based on repeated samples due to the high variability of albumin excretion in the urine, the vast majority of studies of microalbuminuria in

hypertensive subjects have been based on single measurements.[13] Therefore; exact prevalence of microalbuminuria in essential hypertensive subjects is still unknown.

The purpose of this study was to assess the prevalence of microalbuminuria in essential hypertensive subjects attending out patient clinic at tertiary care center. We studied 100 hypertensive patients (group A) and 100 age and sex matched normotensive controls (group B) as per the inclusion criteria. Apart from assessing the prevalence of microalbuminuria in essential hypertensive subjects we also studied the correlation of microalbuminuria with severity of hypertension and association of microalbuminuria with target organ dysfunction.

In the present study, sociodemographic profile was comparable in both the groups. Average systolic blood pressure, diastolic blood pressure and mean arterial pressure were significantly higher in hypertensive group. On comparison of laboratory parameters, average serum cholesterol and LDL were significantly higher and HDL was significantly lower in hypertensive group as compared to control group (p value < 0.1). These results were in accordance with the study done by Shasha Yu et al on treatment naive newly diagnosed hypertensive patients. In this study, 34.5 % had borderline high total cholesterol, 19.2 % had high total cholesterol, 11.4 % had low high-density lipoprotein cholesterol and 37.4 % had high non HDL-C.[14] Similar results were obtained in a study done by Zanchetti A on 5376 hypertensive individuals in Italy.[15] Blood urea, serum creatinine and serum uric acid were significantly higher in hypertensive group (p value < 0.001). In the study done by Lin CS, hyperuricemia was found in 35% hypertensive males and 43% hypertensive females.[16] Serum potassium, serum phosphate and average estimated GFR was significantly higher in hypertensive group (p value 0.001). Similar results were obtained in a study done by S Jalal et al.[17] These results reflect the ongoing renal dysfunction in patients with hypertension.

Out of 100 hypertensive subjects; 47 had microalbuminuria, so the prevalence of microalbuminuria in essential hypertensive subjects was 47% in our study possibly pointing towards the subclinical and subtle changes happening in the glomeruli of these patients. The prevalence of microalbuminuria is not well established and it may vary from 15 to 100%.[18] This variation is probably due to differences in age, race, severity of hypertension and coexistent renal disease in the study populations and different methods of measuring urine albumin. In MAGIC study prevalence of microalbuminuria was 6.7%.[6] B Hithal et al found prevalence of microalbuminuria to be 26.67% in Indian hypertensive patients.[19] The overall prevalence of microalbuminuria in more than 20,000 individuals from 26 countries was 58% in i-SEARCH global study by Bohm et al.[20]

There was a positive correlation between severity of hypertension and urine albumin excretion which is consistent with the previous studies done by Hsu et al[21] and Ibsen et al[22]. End organ damage as manifested by decreased eGFR, ECG change and hypertensive retinopathy was significantly higher in microalbuminuric group and vice versa 24 hours mean urine albumin excretion was significantly higher in hypertensive patients with end organ damage. Dyslipidemia was significantly higher in microalbuminuric hypertensive subjects when compared to normoalbuminuric hypertensive subjects. Similar results were obtained in Gubbio population study done by Cirillo et al.[23] In hypertensive group; subjects with microalbuminuria were older than those with normal albumin excretion (p value <0.05). This finding is in agreement with previous studies done by Hillege et al,[24] Klausen et al[25] and Romundstad et al.[26] In a community based study done by Blecker et al, there was a clear trend of a linear relationship between age and albumin excretion in the urine[151].

Several studies have indicated that the presence of proteinuria or microalbuminuria is an independent predictor of cardiovascular morbidity and mortality in patients with essential hypertension.[27,28] We demonstrated cardiomegaly on chest x-ray, LVH and ischemic changes on ECG in significant number of patients with microalbuminuria compared to hypertensive patients with normoalbuminuria.

Conclusions

In summary, our data suggest that microalbuminuria is prevalent in 47% of patients with essential hypertension and has a positive correlation with the severity of hypertension and target organ damage. Early screening for microalbuminuria in patients of essential hypertension and thereby early initiation of treatment might help in reducing the morbidity and mortality.

Limitations of Study

Major limitation of the study was small sample size of 100 subjects. Due to cross sectional nature of the study we could not evaluate albuminuria over time, effect of antihypertensive therapy and further occurrence of cardiovascular events and their correlation with microalbuminuria. Further prospective studies with large study population are needed to confirm the findings of this study.

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