

## Research Article

# Microalbuminuria as an overrated indicator of target organ damage in hypertension: a hospital based cross sectional study

Bidita Khandelwal<sup>1\*</sup>, Dheeraj Khatri<sup>1</sup>, Swarup Kr. Patnaik<sup>1</sup>, Mingma L. Sherpa<sup>2</sup>, Sumit Kar<sup>3</sup>

<sup>1</sup>Department of Medicine, Sikkim Manipal Institute of Medical Sciences, Tadong, Gangtok-737102, Sikkim, India

<sup>2</sup>Department of Biochemistry, Sikkim Manipal Institute of Medical Sciences, Tadong, Gangtok-737102, Sikkim, India

<sup>3</sup>Department of Community Medicine, Sikkim Manipal Institute of Medical Sciences, Tadong, Gangtok-737102, Sikkim, India

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### \*Correspondence:

Dr. Bidita Khandelwal,

E-mail: drbidita@gmail.com

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## ABSTRACT

**Background:** Hypertension is one of the leading causes of global burden of disease. Uncontrolled hypertension is associated with long term risk of damage to vital organs like brain, heart, kidney, blood vessels and eye i.e. Target Organ Damage (TOD). Medical scientists all over the world have been in search for an indicator which can accurately predict TOD. It is accepted that Microalbuminuria (MA) represents a more generalised vascular problem, not only confined to renal microcirculation. MA is found in a significant proportion of non-diabetic population, particularly in association with hypertension and is a predictor of cardiovascular disease. The objective of the study was to evaluate MA in hypertension and its correlation with TOD.

**Methods:** A Hospital based cross sectional study carried out in the department medicine of central referral hospital, a well-equipped tertiary care hospital in East Sikkim, Gangtok. 200 patients were recruited fulfilling the inclusion criteria of pre hypertension, stage 1 & 2 hypertension as defined by JNC 7 report. Patients with secondary hypertension, DM, ESRD & hyperuricemia were excluded. MA was estimated by Immunoturbidimetry.

**Results:** MA is associated with all TOD but significant correlation was found only with retinopathy. Out of 200 study subjects, 90 (45%) subjects had retinopathy out of which 54 (60%) had MA and 36 (40%) did not have MA. (P <0.0001)

**Conclusion:** MA has established its position in DM where it indicates early end organ damage and heralds cardiovascular risk. Its role as a reliable indicator of TOD in non-diabetic hypertensives needs further evaluation.

**Keywords:** Hypertension, Microalbuminuria, Retinopathy

## INTRODUCTION

Hypertension is one of the leading causes of the global burden of disease. Hypertension doubles the risk of cardiovascular diseases, including Coronary Heart Disease (CHD) and Congestive Cardiac Failure (CCF). It also increases the risk of ischemic and hemorrhagic stroke, renal failure, and peripheral arterial disease. Uncontrolled and long standing hypertension is

associated with long term risk of damage to vital organs like brain, heart, kidney, blood vessels and eye i.e. Target Organ Damage (TOD). During the last few decades medical scientist all over the world have been in search for an indicator which can accurately predict target organ damage. Studies conducted elsewhere rates Microalbuminuria (MA) as a promising indicator for TOD. MA is an early marker of diffuse target organ damage in essential hypertension and therefore can be used to identify patients for whom strategies that are

more aggressive be planned. With the said background, the present study is undertaken to find whether MA is a reliable or an overrated indicator of TOD in hypertension.

## **METHODS**

A hospital based cross sectional study was carried out in a tertiary care hospital in Gangtok East Sikkim during the study period 1<sup>st</sup> November 2011 to 31<sup>st</sup> October 2012. A total of 200 patients admitted in central referral hospital under dept. of medicine and fulfilling the inclusion criteria were recruited for the study.

### ***Inclusion criteria***

Pre hypertension, stage 1 & 2 hypertension as defined by JNC 7 report.

### ***Exclusion criteria***

Patients with secondary hypertension, diabetes mellitus, end stage renal disease & hyperuricemia were excluded from the study.

Institutional ethics committee approved the study. All the subjects were explained about the purpose of the study and were ensured strict confidentiality. Written informed consents were taken from each of the participants before the study. Following Helsinki declaration on research bioethics, the participants were given the option not to participate in the study if they wanted otherwise.

### ***Operational definition***

MA is defined as Urinary Albumin Excretion (UAE) in the range of 20-200 µg/min or 30-300 mg/24 hours or 30-300 mg/L in a spot sample

### ***Data collection procedure***

The primary investigator collected the data using a pre-designed pretested questionnaire designed at the institute with the help of experts from various departments. A detailed history was recorded, a thorough clinical examination done and relevant laboratory investigation performed. The main outcome variables were MA in urine and its relation to target organ damage

All variable of MA was estimated in department of biochemistry by quantitative method. 5 ml of spot midstream urine sample was collected in a sterile vial for the estimation of MA. Immunoturbidimetry. In this method albumin in the urine sample forms an insoluble complex with antibodies to human albumin. PEG accelerates complex formation. The turbidity caused by the complexes is then spectrophotometrically measured at 340 nm to get a measure of albumin concentration. The background absorbance of the initial urine sample is automatically subtracted. This method is simple, less

expensive and rapid analysis of large number of samples is possible.

### ***Statistical analysis***

The data collected were thoroughly cleaned and entered into Microsoft excel spreadsheets and analysis was carried out. The procedures involved were transcription, preliminary data inspection, and interpretation statistical analysis was done with the help of percentage (%) and Chi-square. Variables are represented in the form of percentage (%), whereas Chi-square was done for quality variable and p value of <0.05 was considered to be significant; Chi-square was estimated by InStat graphpad software.

## **RESULTS**

Among 200 patients enrolled in the study 72 (36%) had MA while 128 (64%) did not have MA. Among those who had MA, 38 (52.78%) were males and 34 (47.22%) were females. Majority of the study participants were in the age group 60-69 years followed by 30-39 years. Males and females separately were also highest in this group, being 32 and 24 respectively. There were no females in age group <30 years and ≥90 years.

Out of 200 enrolled subjects, there was a predominance of Nepali population, which comprised of 132 (66%) individuals out of which 48 (36.36%) subjects had MA and 84 (63.63%), did not have MA. There were 30 participants from Bhutia community of which 14 (46.66%) had MA, while 16 (53.33%) did not have. Among the 32 Lepcha subjects enrolled, 10 (31.25%) had MA while 22 (68.75%) did not have. Urban population in study group who had MA and who did not have, were 42 (38.88%) and 66 (61.11%) respectively. In the rural population of the study group, 30 (32.60%) and 62 (67.39%) had and did not have MA respectively. MA was found in 40 subjects (37.73%) with normal BMI (18.5-24.9), 28 subjects (31.11%) with overweight (BMI: 25-29.9), and 4 subjects (100%) with obesity (BMI >30).

On evaluating the relation between MA and TOD in hypertension the following results were obtained: Among all participants 90 (45%) cases had retinopathy, which is an important early marker of target organ damage in hypertension, fifty four 54 (60%) of cases with retinopathy had MA. Among these, 28 patients had grade 1 retinopathy and 26 patients had grade 2 retinopathy. The occurrence of retinopathy with MA was found to be statistically significant (P <0.0001). Similarly 52 (26%) participants were having Central Nervous System (CNS) involvement out of which 26 (50%) had MA. Patients with hypertensive bleed accounted for 18 cases out of which 6 had MA and 12 did not have MA. Patients with hypertensive infarct accounted for 34 cases out of which 18 had MA and 16 did not have MA. No statistically significant relationship between MA and cerebrovascular involvement (P = 0.14) was observed. On analysis of the

52 (26%) subjects having significant Cardiovascular System (CVS) involvement. 22 (42.30%) subjects were found to have MA among which 17 subjects were having Left Ventricular Hypertrophy (LVH) and 5 subjects had diastolic dysfunction. Those having CVS involvement without MA had CCF, LVH, diastolic dysfunction, Myocardial Infarction (MI) and Atrial Fibrillation (AF).

There was no significant statistical correlation between MA and cardiovascular involvement ( $P = 0.59$ ). On analyzing the relationship between MA and Lipid derangement it was observed that 16 (8%) of study participants had dyslipidemia, out of which 4 (25%) had MA. There was no significant relationship between MA and dyslipidemia ( $P = 0.77$ ).

**Table 1: depicting the relation of microalbuminuria to target organ damage.**

Target organs	Urine for MA <30 mg/l N=128 n (%)	Urine for MA ≥30 mg/l N=72 n (%)	Total N=200 n (%)	Statistical analysis
<b>Eye involvement</b>				
Retinopathy (+ve)	36 (40%)	54 (60%)	90 (45%)	$\chi^2 = 18.6$ , df 1, $P < 0.0001$ , RR = 0.48, CI = 0.33-0.70
Retinopathy (-ve)	92 (83.63%)	18 (16.36%)	110 (55%)	
<b>Cerebrovascular system</b>				
CNS (+ve)	26 (50%)	26 (50%)	52 (26%)	$\chi^2 = 2.224$ , df 1, $P = 0.14$ , RR = 0.73, CI = 0.48-1.09
CNS (-ve)	102 (68.91%)	46 (31.08%)	148 (74%)	
<b>Cardiovascular system</b>				
CVS (+ve)	30 (57.69%)	22 (42.30%)	52 (26%)	$\chi^2 = 0.29$ , df 1, $P = 0.59$ , RR = 0.87, CI = 0.60-1.26
CVS (-ve)	98 (66.21%)	50 (33.78%)	148 (74%)	
<b>Lipid disarrangement</b>				
Dyslipidemia (+ve)	12 (75%)	4 (25%)	16 (8%)	$\chi^2 = 0.09$ , df 1, $P = 0.77$ RR = 1.19, CI = 0.77-1.82
Dyslipidemia (-ve)	116 (63.04%)	68 (36.95%)	184 (92%)	

## DISCUSSION

The present study reflects that among the enrolled participants, 72 (36%) had MA while 128 (64%) did not have. Participants from Bhutia community had more chances of developing MA 14 (46.66%) as compared to Lepcha subjects 10 (31.25%). MA was found in 40 subjects (37.73%) with normal BMI (18.5-24.9), 28 subjects (31.11%) with overweight (BMI: 25-29.9), and 4 subjects (100%) with obesity (BMI >30). On evaluating the relation between MA and TOD in hypertension it was seen that 60% cases with retinopathy had MA. Similarly 50% of cases with CNS involvement, 42.30% subjects with CVS involvement and 25% of study participants with dyslipidemia were found to have MA. Significant statistical association was seen between presence of MA and occurrence of retinopathy ( $P < 0.0001$ ). However these relation doesn't hold good for other target organ damage.

### MA and retinopathy

Similar observation regarding MA and retinopathy in HTN was made by Biesenbach et al. (Magic study) where they have found significant correlation of MA and retinopathy. They concluded that patients who had MA despite effective antihypertensive treatment showed a significantly higher prevalence (85%) of hypertensive retinopathy (grades I and II) compared to patients with

reversible MA (36%) and to normoalbuminuric patients (31%). Moreover the prevalence of persistent MA was significantly higher in the patients with hypertensive retinal changes.<sup>1</sup>

There has been another study showing a significant correlation between MA and retinopathy ( $P < 0.001$ ) by Sharan Badiger et al. which was done in 2012 on 100 patients. Tests show that hypertension is mostly associated with retinopathy of grade 2 (35%) followed by grade 1 and grade 3 (14%) each.<sup>2</sup>

Bhaskar E et al., in study of 180 elderly hypertensive patients concluded that MA had a strong association with hypertensive retinopathy ( $P < 0.0001$ ). Tests for accuracy for hypertensive retinopathy as a predictor of microalbuminuria showed a sensitivity of 72% & specificity of 82%.<sup>3</sup>

However Cuspidi C et al. have mentioned in their study that advanced retinopathy is a rare finding in non-diabetic hypertensive patients with microalbuminuria. Their study indicated that advanced retinopathy is a rare finding in non-diabetic hypertensive patients seen in a specialist setting and a strong relation exists between retinal microvascular lesions and cardiac and macrovascular markers of TOD but not with MA.<sup>4</sup>

### **MA and central nervous system involvement**

The relationship between MA & CNS involvement in hypertensive patients has been reported differently by different workers. The results of this study are depicted in the table. There were no patients with cognitive impairment and dementia. The p value derived was not significant statistically ( $P = 0.14$ ). So this study does not show significant relation between CNS involvement and MA. Sharan Badiger et al. in their study of 100 patients of essential hypertension in 2012 did not show any correlation between MA and hypertensive stroke.<sup>2</sup>

Gumbinger C observed that MA was frequently found in acute ischemic stroke patients and was a potential marker between them.<sup>5</sup> Nancy B et al. concluded that MA was 3 times more prevalent in patients with recent stroke. The results of their study confirm an earlier report of no significant difference in the prevalence of MA among different subtypes of stroke. However, in patients with a history of recent or remote stroke or transient ischemic attack, MA was an independent marker for future stroke ( $P < 0.0001$ ), even after correction for the above risk factors. Thus, although identification of markers for individuals at increased risk for stroke has been problematic, these data support the view that MA merits further scrutiny as a potentially inexpensive and easily measured marker for heightened risk of stroke in patients who had MA.<sup>6</sup> A case-control study by Woo J et al. found that the highest level of MA values was associated with a 13 fold increased risk for stroke.<sup>7</sup> Umemura et al. in their study which comprised of 285 individuals observed that MA is closely associated with the prevalence of deep or infratentorial Brain micro bleeds in hypertensive patients.<sup>8</sup>

### **MA and cardiovascular system**

On analyzing the relation of MA and CVS involvement in hypertension, no significant correlation was observed. Palatini P et al. in their study which comprised of 870 patients (628 men and 241 women) had failed to show any correlation between albumin excretion rate and LVH.<sup>9</sup> Nancy B et al. in their study of 121 individuals were not able to demonstrate any correlation between MA and LVH.<sup>6</sup>

Contrary to our observations, Leoncini G et al. had observed that hypertension with microalbuminuria had 20 folds increase in both left ventricular hypertrophy and carotid wall abnormalities.<sup>10</sup> Monfared A et al. showed relation between left ventricular hypertrophy and microalbuminuria in patients with essential hypertension. Patients with LVH had significantly higher microalbuminuria level compared with those without LVH.<sup>11</sup> Andrikou E et al. Showed Left Ventricular Mass Index (LVMI) as a predictor of new onset microalbuminuria in hypertensive subjects which revealed that increase of LVMI leads to 15% increased risk of MA.<sup>12</sup> Mahfoud F et al. demonstrated that

Microalbuminuria (MA) is a marker for endothelial dysfunction and a predictor of cardiovascular events and showed that the number of co morbidities increase with increase in albuminuria.<sup>13</sup>

### **MA and lipid profile**

There was no significant correlation between MA and dyslipidemia ( $P = 0.77$ ). The findings are similar to that of Sharan Badiger et al. who have not mentioned any significant correlation between MA and dyslipidemia.<sup>2</sup> However many studies have shown relationship between MA and dyslipidemia, Borgai et al. observed that microalbuminuria has been associated with lipid abnormalities, including high levels of Low Density Lipoprotein Cholesterol (LDL-C) and triglycerides, low levels of HDL-C, and elevated levels of lipoprotein.<sup>14</sup> Mimran et al. observed that in patients with hypertension the combined presence of microalbuminuria and hyperlipidemia is common and greater levels of albuminuria correlates with serum level of triglycerides and apolipoprotein B and low LDL cholesterol.<sup>15</sup> Jensen et al. have described low levels of apolipoprotein A1 and HDL cholesterol in patient with microalbuminuria.<sup>16</sup> Bianchi et al. have shown greater serum levels of low density lipoprotein cholesterol and lipoprotein A and a greater LDL-HDL ratio in hypertensive patient with microalbuminuria which can be an indicator of renal disease.<sup>17</sup>

### **CONCLUSION**

MA has established its position in evaluation of diabetic patients but its role in HTN needs further evaluation. In this hospital based cross sectional study of 200 hypertensive subjects, it was observed that MA is associated with all TOD but there was no significant correlation between them except with retinopathy. Retinal changes of any grade probably have moderate accuracy in predicting MA & hence we can initiate work up for TOD in cases of HTN when retinopathy is present. Accurate risk evaluation is a pre requisite for devising cost effective therapeutic strategies to reduce the burden of the disease. Screening for MA is simple, efficient, reproducible and non-invasive but its reliability and significance as an indicator of TOD in HTN needs to be established before including it in regular workup of HTN.

### **Limitation of study**

Studies in various parts of India have been undertaken to study the relationship of MA & TOD in hypertension but this is first of its kind in Sikkim. Mukhopadhyay B et al. in 1996 observed the prevalence of HTN to be 15% to 42% in Lepcha population of Sikkim but they did not evaluate the subjects for TOD. This being a tertiary care paying hospital there is always a possibility of differential presentation of patients depending on health consciousness & affordability and the findings cannot be extrapolated to the general population. Long term



prospective studies are needed to establish the importance of MA as an independent predictor of TOD in non-diabetic hypertensive patients. The study can act as a revelation for more research in this field.

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