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Correlation of Microalbuminuria with Duration and Severity of Systemic Hypertension

Dr. Sobu Mathews[1], Dr. Teena Mary Varghese [2]
[1]Assistant Professor, Department of Internal Medicine, SUT Medical College Vattapara, Kerala, India, [2] Senior Resident, Department of Internal Medicine, SUT Medical College Vattapara, Kerala, India

Abstract
Introduction:
Hypertension is a major burden of disease all over the world, especially in India. It is also sometimes known as the 'silent killer'. Essential hypertension produces proteinuria and thereby, severe reduction in renal function in at least 5 – 15% of patients. Urinary albumin excretion ranging from 30 -300 mg/day (i.e.microalbuminuria) is found in many number of patients with hypertension. The recent interest in microalbuminuria is due to the fact that there have been many recent studies which showed that microalbuminuria is an independent risk factor for cardiovascular disease and worsening renal disease.
Material and Methods: *Descriptive study done in a tertiary health care centre of 260 patient with essential hypertension. The patients satisfying the inclusion criteria were included till the sample size was met*
All patients with history of hypertension on treatment and newly detected hypertension who met the inclusion criteria were included in the study after obtaining written informed consent. Average of two blood pressure recordings made with a sphygmomanometer was taken as the blood pressure of that particular patient. Microalbuminuria was detected by the albumin – creatinine ratio in an early morning urine sample. A detailed case record was made recording the duration, the blood pressure recording and the treatment for hypertension. Statistical analysis was done using the Chi-square test, to determine the association between microalbuminuria and the duration and severity of hypertension. A p value of less than 0.05 was considered significant.
Results: *The prevalence of microalbuminuria in our study population was found to be* ***48.5%*** *which is comparable to other studies done in the past. In our study, microalbuminuria was found in 60.2% of patients with Stage 2 hypertension* ***(p = 0.036)*** *as compared to 43% of patients with Stage 1 and 45.5% with Pre-Hypertension. It was also seen that the prevalence of microalbuminuria correlated with the duration of hypertension, 66.7% in patients who had hypertension for more than 10 years* ***(p=0.023)*** *as compared to 47% of patients with hypertension for less than 5 years and 42.5% in patients with hypertension between 5 and 10 years. This positive relation of microalbuminuria with severity and duration of hypertension is consistent with prior studies done in this regard.*
Conclusion: *Microalbuminuria is a significant accompaniment of hypertension (48.5%) in our population and it has statistically significant positive correlations with duration and severity of hypertension. Adequate measures to control hypertension and to make the general population aware of this entity of microalbuminuria is of paramount importance.*
Keywords : *Microalbuminuria , Duration of Hypertension, Stage of hypertension*

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I. Introduction

Hypertension is one of the most common diseases afflicting humans worldwide and is a major risk factor for stroke, myocardial infarction, vascular disease, and chronic kidney disease. Hypertension, or the silent killer as it is often called, is defined as a systolic blood pressure (SBP) of 140 mm Hg or more, or a diastolic blood pressure (DBP) of 90 mm Hg or more, or taking antihypertensive medicines [(1).] Based on recommendations of the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7), the classification of BP for adults aged 18 years or older has been as follows [[2]] •Normal: Systolic lower than 120 mm Hg, diastolic lower than 80 mm Hg
•Prehypertension: Systolic 120-139 mm Hg, diastolic 80-89 mm Hg
•Stage 1: Systolic 140-159 mm Hg, diastolic 90-99 mm Hg
•Stage 2: Systolic 160 mm Hg or greater, diastolic 100 mm Hg or greater.

2017 ACC/AHA Guidelines

The new ACC/AHA guidelines (2017) have omitted the entity of Prehypertension and simply divides it into three levels : [3]

(1) **Elevated BP,** with a systolic pressure (SBP) between 120 and 129 mm Hg and diastolic pressure (DBP) less than 80 mm Hg, and

(2) **Stage 1 hypertension**, with a SBP of 130 to 139 mm Hg or a DBP of 80 to 89 mm Hg.

(3)**Stage 2 hypertension** , with a SBP >140 mmHg or a DBP > 90 mmHg.

Microalbuminuria: It has been 200 years since the phenomenon of albuminuria was described. Its associated with kidney disease was described by Richard Bright in 1827[4]. Microalbuminuria is defined as urinary albumin excretion of 30-300 mg/day. It is an early sign of vascular damage. It is a marker of general vascular dysfunction and is nowadays considered a predictor of worse outcomes for both kidney and heart patients. There is a significant correlation between blood pressure and microalbuminuria. Even high normal blood pressure is associated with significant higher frequency of microalbuminuria. In this way it has now become a biomarker of increased cardiovascular risk. Not that microalbuminuria causes cardiovascular disease directly, but it serves as a marker to identify those who are at increased risk. Microalbuminuria results from glomerular capillary injury and so may be a pointer towards diffuse endothelial injury [5]. According to the Steno hypothesis, albuminuria might reflect a general vascular dysfunction and leakage of albumin and other macromolecules into the vessel wall may trigger inflammatory and then atherosclerotic processes [6] In the US, approximately 6 and 9.7% of men and women respectively have microalbuminuria. A positive link has been observed between hypertension and microalbuminuria. High blood pressure causes increased glomerular filtration pressure, thereby causing microalbuminuria. It is possible that increasing blood pressure causes higher pressure in the glomerular and peritubular capillaries, and thus causes changes in tubular albumin processing [4] Given the such serious implications of microalbuminuria, it is important to recognise the need to control it in our patients. As we continue to gain more evidence, it has recently been shown that levels lower than the classical microalbuminuria range, that is even levels of albumin excretion, falling into the high normal range of albuminuria, is associated significantly with vascular diseases and hence, there are recommendations saying that the term microalbuminuria itself should be removed and albuminuria even in small levels should be targeted.[7] It should be remembered that every halving of albumin excretion is associated with 18% reduction of cardiovascular risk. Screening for microalbuminuria remains the most effective way to identify people who are at risk for renal and cardiovascular disease. Albumin dipstick method which is available in most hospitals at bedside is probably the most efficient method of initial screening. In general, agents that act on the renin angiotensin aldosterone system (ARBs and ACEIs) slow the progression to overt nephropathy. All measures that reduce albuminuria such as reduction of insulin sensitivity, weight loss, reduction of blood pressure and glucose levels and RAS inhibition will help to prevent or delay end organ damage.

II. Material and Methods

Study Design: Descriptive study done in a tertiary health care centre in Kerala.

Study Population: All patients with essential hypertension

Inclusion Criteria: All patients above the age of 18yrs with essential hypertension (both newly diagnosed and on treatment for hypertension) attending the Medicine OPD and those getting admitted to the medicine wards of Sree Gokulam Medical College and Research Foundation, Venjarammood, Trivandrum during the time period of 2 years from January 2017 to January 2019.

Exclusion Criteria: Patients with Type 2 DM, Patients with documented Chronic Kidney Disease, Patients with macroalbuminuria, Congestive Cardiac Failure, Active Urinary Tract Infection

Outcome Variables Presence of microalbuminuria in the study population

Sample Size: Sample size **– 260**

$$\mathbf{n = Z^2\ 1 - \alpha / p\ (\ -\ p)}$$

$$\mathbf{d^2}$$

α = 5%; Z – α/ – 1.96 ; p = 27% [8]

d = 20% of p So, n = 260

Sampling Technique: Consecutive patients satisfying the inclusion criteria were enrolled for the study till the sample size was reached.

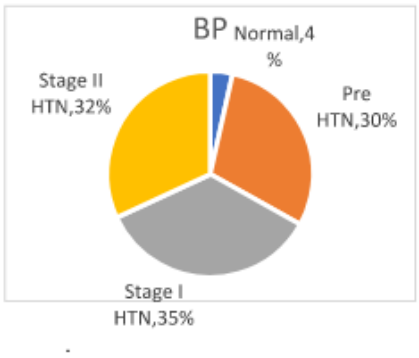
Data Collection: Patients were included in the study after a written informed consent and after the study was approved by the institutional review board.

Each participant was interviewed with the help of a structured questionnaire and examined in detail. The blood pressure of each patient was measured using the auscultatory method with a standardized mercury sphygmomanometer with an appropriately sized cuff in the seated posture with feet on the floor and arm supported on table at heart level. An average of two blood pressure recordings 5 minutes apart was taken as the BP of that individual. A detailed case record was prepared for each patient on a preformed study sheet. The details of hypertension and its duration with the details of treatment taken, if any, was taken in addition to history of cardiovascular symptoms like angina, palpitations and dyspnoea, neurological symptoms like headache, TIA, seizures or previous stroke and visual symptoms like blurring and/or dimness of vision.
Microalbuminuria was assessed by urine albumin-creatinine ratio (ACR) based on the recommendations of the National Kidney Foundation and the American Diabetic Association. Urine albumin was estimated by turbidimetry. 5ml of first – voided, early morning sample of urine was used. In women, urine examinations was done during the non- menstrual phase of their cycles.
ACR value between **30 – 300 mg/day** was taken as microalbuminuria.
During the study period there was no deviation from standard of care and no extra investigations were done for the purpose of research.
Statistical Analysis: Qualitative variables will be expressed as frequency and percentage. For testing the association between microalbuminuria and the duration and severity of Hypertension, Chi – square test was done. A p value of less than 0.05 was considered significant.
Operational Definitions: Microalbuminuria (MA) is defined as urinary albumin excretion of 30 – 300 mg/day.
Hypertension was graded in severity according to the JNC 8 Classification of hypertension.

III. Results

The mean age of patients studied was 64.13. The maximum number of patients were in the age group of 61 – 70 yrs (33.5%). A slightly higher number of the study population were males (55%) as compared to women (45%)

Table 1: *Severity of hypertension in the study population*: The majority of patients studied had only Stage 1 Hypertension(35%), closely followed by Stage 2 Hypertension (31.9%). It is interesting to note that 29.6% of the patients had Pre Hypertension



BP	Frequency	Percent
Normal	9	3.5
Pre HTN	77	29.6
Stage I HTN	91	35.0
Stage II HTN	83	31.9
Total	260	100.0

Table 2: *Frequency of microalbuminuria:* The frequency of our study in the population was 48.5 %

Microalbuminuria	Frequency	Percent
Yes	126	48.5
No	134	51.5
Total	260	100.0

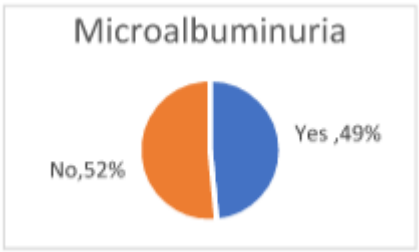
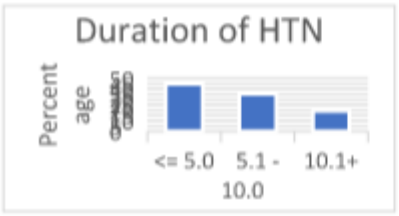


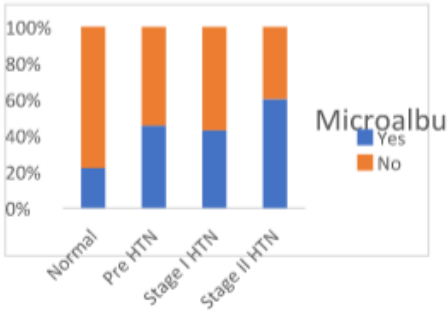
Table 3: *Total duration of the disease:* Around 45% of the patients studied had hypertension for less than 5 years. 35.5% of the patients had a duration between 5 – 10 years and only around 20% of them had hypertension for more than 10 years.



Duration of HTN in years	Frequency	Percent
≤ 5.0	110	44.9
5.1 - 10.0	87	35.5
10.1+	48	19.6
Total	245	100.0

Table 4: *Frequency of Microalbuminuria based on the different stages of hypertension*

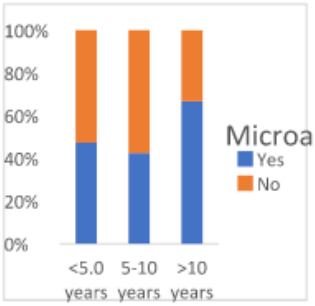
In our study it was seen that microalbuminuria was present in 60.2% of patients with Stage 2 Hypertension**(p= 0.036),**in 43% with Stage 1 Hypertension and in upto 45.5% with Pre Hypertension. That is, microalbuminuria was proportional to the stage of hypertension.



HTN	Microalbuminuria				Total	
	Yes		No			
	N	%	N	%	N	%
Normal	2	22.2	7	77.8	9	100.0
Pre HTN	35	45.5	42	54.5	77	100.0
Stage I HTN	39	42.9	52	57.1	91	100.0
Stage II HTN	50	60.2	33	39.8	83	100.0
Total	126	48.5	134	51.5	260	100.0

χ^2 =8.515 df=3 p=0.036

Table 5*: Frequency of microalbuminuria based on the duration of hypertension*



Duration of HTN	Microalbuminuria				Total	
	Yes		No			
	N	%	N	%	N	%
<5.0 years	52	47.3	58	52.7	110	100.0
5-10 years	37	42.5	50	57.5	87	100.0
>10 years	32	66.7	16	33.3	48	100.0
Total	121	49.4	124	50.6	245	100.0

χ^2 =7.568 df=2 p=0.023

In our study, it was seen that the frequency of microalbumiuria increased with the duration of hypertension (66.7% in patients > 10 years – **p=0.023**) 47% of patients with hypertension for less than 5 years had microalbuminuria and 42.5% of patients with hypertension between 5 – 10 years had microalbuminuria.

IV. Discussion

Microalbuminuria and vascular dysfunction are known to occur early in the course of essential hypertension. Endothelial dysfunction has been proposed as a possible pathophysiological mechanism of microalbuminuria.[9] Several studies done in the past have showed that the presence of microalbuminuria is an independent predictor of cardiovascular morbidity and mortality in patients with hypertension.[10,11]

This study was done to determine the prevalence of microalbuminuria in the hypertensive patients attending the medical OPD and wards of Sree Gokulam Medical College and Research Foundation. The prevalence of microalbuminuria among hypertensives has not been well established and may range anywhere from 15 – 50%.[12]

- **Comparison of prevalence of microalbuminuria**

Pontremoli R et al	6.7%
Bohm et al	58.4%
B. Hithal et al	26.67%
H.K Aggarwal et al	47%
Shankar Radhakrishnan et al	64%
Praveen Kumar Tagore et al	23.21%
Ana Maria et al	13.7%
Muhammad Yakoob Ahmadani et al	24.2%
Anil Kumar H et al	32%
Present study	**48.5%**

There have been many studies in the past both from India and abroad looking at the prevalence of microalbuminuria. The MAGIC study by Pontremoli R et al from Italy showed a prevalence of 6.7% among 787 patients studied. [(13)] Another large and probably the largest study done among more than 21,000 individuals from 26 countries was the i-SEARCH global study done by Bohm et al from Germany, which recorded a prevalence of microalbuminuria at 58.4%. [(14)] B. Hithal et al in their study showed a prevalence of 26.67% from South India. [(15)] A study done by H.K. Aggarwal et al from Rohtak, Haryana showed a prevalence of 47% [(16)] The study by Shankar Radhakrishnan et al from Salem, Tamil Nadu showed a prevalence of 64%. [(17)] In their study on 112 patients, Praveen Kumar Tagore et al from Gwalior, Madhya Pradesh saw the prevalence of microalbuminuria to be 23.21%. [(18)] In another study done from South Brazil among 153 patients by Ana Maria et al , the prevalence of microalbuminuria was estimated as 13.7% [(19)] Muhammad Yakoob Ahmadani et al from Pakistan , in their study on 153 patients with hypertension and Type 2 DM found the prevalence of microalbuminuria to be 24.2% [(20)] In another study from South India, Bangalore, Anil Kumar H et al found a prevalence of 32% for microalbuminuria among 50 patients with essential hypertension. [(21)]
The prevalence of microalbuminuria in our study was **48.5%**, which was similar to the prevalence noted by H K Aggarwal et al from Haryana. Another interesting fact that was noted on comparison among different studies was that the prevalence of microalbuminuria in other parts of the world, especially, European countries from where we have comparative studies, are really very low compared to the Indian data. Even among data from India, the data from studies done in Southern India show a higher prevalence than those done in the North. Accepting the fact that the number of patients and their baseline characteristics are different, this prompts us to think in terms of a genetic basis for microalbuminuria.

- **Comparison of severity of hypertension in the study population:**

The present study had majority of Stage I hypertensives and that constituted only 35% of the study population. One of the causes for this might be that we had taken into account all patients with hypertension and in our study, 29.6% of patients had Pre Hypertension.

Name of investigator	**Stage of Hypertension**	**Percentage**
Ana maria et al	Stage I	46%
Praveen Kumar Tagore et al	Stage II	80%
H K Aggarwal et al	Stage I	85%
R Habbal et al	Stage I	76.8%
Present study	**Stage I**	**35%**

And also, we also had patients on treatment for hypertension and not treatment-naïve patients. These might be the contributory causes for the low percentage of the majority of hypertensives. According to Mimran et al [(22)] microalbuminuria was higher in normotensive individuals with just a positive family history of hypertension. Systolic arterial pressure was also mentioned as an important contributory factor in microalbuminuria. He also mentioned that both in normotensive patients and in patients with essential hypertension, overweight was significantly associated with microalbuminuria. S Basi et al [(23)] stated that the slope between systolic arterial pressure and hypertension is steeper in males than in females. The level of microalbuminuria remained unaltered within the normotensive range (SBP ≤140mmHg). It was observed that the slope of the relationship between systolic arterial pressure and microalbuminuria increased with increasing dietary sodium intake. Some of the factors other than systolic blood pressure that are known to influence

microalbuminuria are obesity, insulin resistance and smoking. The influence of obesity and insulin resistance on microalbuminuria point towards the fact that microalbuminuria may be linked to the metabolic syndrome. It has been reported that the prevalence of microalbuminuria is higher in patients with metabolic syndrome. [(24)] The mean duration of hypertension in most of the studies were comparable. The mean duration of hypertension of the maximum number of patients in our study was 7.5 years.

- **Comparison of duration of hypertension in the study population**

The mean duration of hypertension in most of the studies were comparable. The mean duration of hypertension of the maximum number of patients in our study was 7.5 years.

Name of investigator	Mean Duration of Hypertension
Shankar Radhakrishnan et al	5 years
Praveen Kumar Tagore et al	6 years
Ravjit Kaur Sabharwal et al [(21)]	5.15 years
Present study	**7.5 years**

- **Comparison of the prevalence of microalbuminuria based on the severity of hypertension**

Name of investigator	Severity of hypertension	Prevalence of MA
B Hitha et al	Stage II Hypertension	40%
Shankar Radhakrishnan et al	Stage II Hypertension	73.6%
H K Aggarwal et al	Stage II Hypertension	93.33%
Present study	**Stage II Hypertension**	**60.2%**

It is very evident from the above table that the prevalence of microalbuminuria increases as the severity of hypertension increases. The findings of our study was consistent with results of studies done in other parts of the country and also other parts of the world. As the severity of hypertension increased, increasing number of patients developed microalbuminuria. Taking into consideration the fact that most of the patients in our study was on treatment for hypertension , the above finding highlights the importance of proper control of hypertension. It is not sufficient on the part of the clinician to start a patient on anti – hypertensives, but it is also his or her responsibility to see that hypertension is properly controlled. Considering the fact that microalbuminuria is an important predictor of future cardiovascular and renal diseases, we should strive to keep patients away from these complications.

- **Comparison of the prevalence of microalbuminuria based on the duration of hypertension**

As seen in many of the above mentioned studies , the prevalence of microalbuminuria increased with increasing age, duration of hypertension and the severity of hypertension.

Name of investigator	Duration of hypertension	Prevalence of MA
Praveen Kumar Tagore et al	>10 years	60%
B Hitha et al	>10 years	16%
Present study	**>10 years**	**66.7%**

This was again seen in the HARVEST study done by Palatini P et al [(25)] The expected increase in microalbuminuria with the duration of hypertension was also studied by B Hitha et al in their study from Kottayam Medical College, Kerala, South India.[(26)]

The other observations of our study like the increasing prevalence of microalbuminuria with age and the increasing microalbuminuria with the male gender have also been studied in various previous studies.

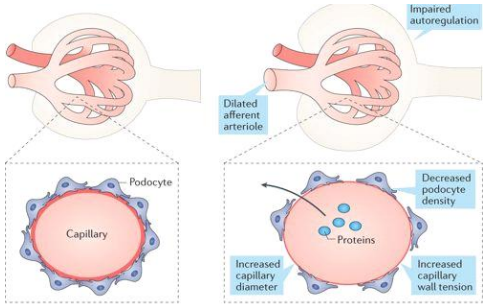
Other observations on microalbuminuria in hypertension:

The reported prevalence of microalbuminuria, as stated earlier, from previous studies done worldwide ranges from 4 – 46%. This wide range may be explained by the intraindividual differences in urinary excretion of albumin, age and ethnicity and discrepancies in measurement of Urine ACR. The main determinant of urinary albumin excretion, especially in patients with mild hypertension and no cardiovascular complications seems to be the hemodynamic load, whereas in patients with more severe hypertension and evidence of target organ damage, the increase in urinary albumin leak is probably due to the glomerular damage.\

Different mechanisms have been described for the development of two of these mechanisms most commonly cited are:

- Increased glomerular hydrostatic pressure
- Increased permeselectivity of the glomerular basement membrane

Normally, elevation of the systemic arterial pressure is associated with vasoconstriction of the afferent arteriole in the glomerulus, which maintains the glomerular hydrostatic pressure unaltered [(27)] This is a natural adaptation to protect the glomeruli from the possible damages of hypertension. When, by any chance, the autoregulatory adaptation of the afferent arteriole is defective, there is elevation of the glomerular hydrostatic pressure. This leads to progressive renal disease. The presence of microalbuminuria in patients with essential hypertension is associated with decreased renal reserve. A study showed significant correlation between urinary albumin excretion and filtration fraction.[(28)]



Microalbuminuria is also dependent on the permeselectivity of the glomerular capillary membrane. Increased production of the vascular endothelial growth factor and vascular permeability factor may contribute to the increased permeability of the glomerular basement membrane for albumin. Vascular permeability factor is implicated in the pathogenesis of microalbuminuria.

Effect of antihypertensive drugs on microalbuminuria:

The greater anti proteinuric effect of ACE inhibitors is due to the selective efferent arteriolar dilatation and a decrease in the intraglomerular hydrostatic pressure caused by these drugs. In addition to these, there seems to be a direct effect of these drugs on the glomerular basement membrane permeselectivity. The anti proteinuric effect of ACE inhibitors is increased by dietary salt restriction and reduced by increasing salt intake.[(29).] The presence of hypertension accelerates the progressive albuminuria and decline in glomerular filtration. Reduction of albuminuria is protective for the development of end stage renal disease, coronary artery disease and cerebrovascular disease. The use of ACE inhibitors or Angiotensin Receptor Blockers leads to larger reduction in albuminuria and decrease the progression of chronic kidney disease.

The present study had findings consistent with other studies on microalbuminuria in hypertension. The effect of the treatment of hypertension on microalbuminuria has not been studied and the prevalence of target organ damage has also not been studied as these were outside the scope of the present study. This study would serve to highlight the importance of blood pressure control and salt restriction in preventing microalbuminuria.This would go a long way, we believe, in reducing the burden of renal and cardiovascular diseases in our community. Screening tools for microalbuminuria need to reach the community at large and the importance of checking for it has to be understood by all in the different levels of health care system in our country.

Patients need to be made more aware regarding the significance of microalbuminuria and proper screening of people who are at risk should be emphasised. The simplicity of diagnosis of albuminuria should prompt the clinician to order for one in patients who are at risk.

V. Conclusion

In this descriptive study done in Sree Gokulam Medical College and Research Foundation, Venjaramood, Trivandrum, among 260 patients with hypertension , the prevalence of microalbuminuria was seen to be 48.5%. There was statistically significant positive correlation between microalbuminuria and the duration and severity of hypertension. Conscious efforts are needed to control hypertension well and to educate the general population regarding this entity of microalbuminuria. This will go a long way in reducing the burden of both renal and cardiovascular diseases in our country.

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