

Association of Microalbuminuria with the Onset of End Organ Damage in Patients with Essential Hypertension

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Abstract:

Background :

Hypertension of long duration especially if not under control leads to damage of retina, kidney, heart and brain. Endothelial dysfunction is considered to be a predominant pathological finding in patients with hypertension. Microalbuminuria, a pathological marker of endothelial dysfunction is frequently elevated in patients with established essential hypertension and is a predictor of a higher risk for cardiovascular disease and renal dysfunction. The presence of microalbuminuria has been shown to correlate with the other cardiovascular risk factors commonly seen in hypertensive patients. This fact indicates that the detection of an increased urinary albumin excretion could be an index of an increased global cardiovascular risk in a given patient. The aim of this study is to evaluate urinary microalbumin in essential hypertensives with and without end organ damage.

Methodology: A total of 255 subjects between the age group of 20-55 years of age, from both sexes who were attending the Hypertensive clinic and Master health check up programme in Sri Ramachandra Medical College were enrolled for the study. They were grouped as three-Group I being controls, Group II hypertensives without complications and Group III hypertensives with end organ damage. After overnight fasting, blood and spot urine samples were collected. All the biochemical parameters were estimated by standard methodologies. Urinary microalbumin was determined by immuno turbidimetric method and creatinine by alkaline picrate method. Albumin Creatinine Ratio (ACR) was also calculated.

Results : Among the hypertensives with end organ damage 71.42% had microalbuminuria, 23.21% had Left Ventricular Hypertrophy (LVH) and 4.44% had Retinopathy. A strong correlation was observed between Systolic blood pressure (SBP) and microalbumin levels in hypertensives with end organ damage. Highly significant correlation was observed between urinary microalbumin level and creatinine in all the groups. Statistical analysis was done using SPSS Software 19.0.

Discussion: 71.42% of the hypertensives with end organ damage had microalbuminuria. A highly significant difference was observed in Urinary creatinine and Albumin Creatinine Ratio (ACR). It is evidenced that renal damage is an early sign of target organ damage in essential hypertensives.

Conclusion: A significant increase in microalbumin levels in essential hypertensives suggests that monitoring the microalbumin levels would be of a great value in assessing the onset of end organ damage.

Keywords: Essential hypertension, Microalbuminuria, Cardiovascular risk

I. Introduction

Hypertension is a major global chronic non communicable disease. One-quarter of the world's adult population has hypertension, and this is likely to increase to 29% by 2025. [1]. It is currently the leading cause of considerable death and disability world wide and accounted for 9.4 million deaths and 7 per cent of disability adjusted life years (DALYs) in 2010 [2] In a population-based study, in rural area of Maharashtra nearly half of the population was in the pre hypertension stage.(Saoner, Nagpur district) [3]. The prevalence of hypertension in the North Indian population is high and varies between 22 and 29%.[4]. In a cross-sectional study conducted in the rural areas of Andhra Pradesh, India, out of 1624 subjects, between the age group of 18-35 years, 30.1% had prehypertension and 7.75% had hypertension [5]. Hypertension is a multifactorial disorder involving any mechanisms leading to cardiovascular, renal, retinal and neurological complications. It is rather a syndrome of arteriosclerosis and renal involvement leading to sodium retention in addition to elevated blood pressure. This fact indicates that the detection of an increased

urinary albumin excretion could probably be the best index of an increased global cardiovascular risk in a given patient. Blood pressure control is accompanied by a fall in the concentration of albumin in urine.

II. Materials & Methods

It is a Case-Control Study. Group I consists of healthy individuals with normal blood pressure without any history of any illness or disease. Group II consists of newly diagnosed hypertensives as well as known hypertensives under control without any evidence of end organ damage viz renal, cardiac, retinal changes and serum creatinine level < 1.2 mg/dl. Group III consists of hypertensives with clinical or laboratory evidence of end organ damage viz renal cardiac, retinal changes and serum creatinine level > 1.2 mg/dl. People taking steroids, oral contraceptive pills and fibric acid derivatives and subjects having diabetes, smokers and chronic alcoholics were excluded from the study.

This study was conducted in hypertensive clinic of General Medicine in Sri Ramachandra Medical College. The study has been approved by the Institutional Ethics Committee (IEC-N1/14/JUN/40/35). Out of 255 samples, 138 belonged to Group I, 61 to Group II and 56 to Group III. The fasting blood and spot urine samples were collected from the subjects after informed consent. The anthropometric measurements were recorded. Serum uric acid was estimated by Uricase method, Blood Urea Nitrogen (BUN) by Urease method and Creatinine by Alkaline picrate method. The urinary microalbumin was determined by immunoturbidimetric method. ACR was calculated as urinary albumin concentration (mg)/ mmol of creatinine

The obtained data were analysed by ANOVA and post hoc test. SPSS Software Version 19.0 was used. P value <0.05 is considered significant.

III. Results

Values Are Expressed As Mean ± SD

Table 1 represents the age and gender distribution among the 3 groups. There is no difference in the mean age between group II & III.

Table 1 : Age and Gender distribution among the 3 groups

Parameters	Group I (n=138)	Group II (n=61)	Group III (n=56)
Age	39 ± 10	49 ± 7	49 ± 6
Female	100	58	50
Male	38	3	6
Female : Male ratio	3:1	19:1	8:1

Table 2 shows the demographic data of 3 groups

Table 2 : Demographic data of the three groups

Parameters	Group I (n=138)	Group II (n=61)	Group III (n=56)	p Value
SBP (mm Hg)	113 ± 9	134 ± 16	137 ± 18	0.0001
DBP (mm Hg)	77 ± 6	85 ± 12	87 ± 10	0.0001
BMI	23.46 ± 3.51	24.57 ± 4.04	25.98 ± 4.60	0.0001

SBP-Systolic Blood Pressure, DBP-Diastolic Blood Pressure, BMI-Body Mass Index
P value <0.05 is considered statistically significant.

There is a significant difference in SBP, DBP and BMI between the groups showing that SBP, DBP and BMI increases as the disease progresses.

Post- hoc tests is done to show the significant difference between the groups. The results are expressed below.

Table 3 : Multiple comparative study showing the significant relationship of the demographic data between the 3 groups

Parameters	Group I & II (n=138,61)	Group II & III (n=61,56)	Group I & III (n=138,56)
SBP mm Hg	0.00001	0.4093	0.0001
DBP mm Hg	0.00001	0.3833	0.0001
BMI	0.2456	0.1630	0.0006

P value <0.05 is considered statistically significant.

There is a highly statistical significant difference in Systolic and Diastolic BP between groups I & II showing that there is marked increase in BP compared to controls. There is no significant difference when hypertensives were compared those with end organ damage. In case of BMI, there is no significant difference when controls were compared against hypertensives without end organ damage as well as hypertensives with

that of end organ damage. A statistically significant difference was observed in case of controls when compared with hypertensives with end organ damage. (Table 4)

Table 4: Biochemical parameters – Renal Profile of the 3 groups

Parameters	Group I (n=138)	Group II (n = 61)	Group III (n = 56)	p Value
BUN (mg/dl)	9.73 ± 3.03	10.03 ± 2.59	10.79 ± 2.90	0.075
Serum Creatinine (mg/dl)	0.72 ± 0.18	0.81 ± 0.21	0.81 ± 0.20	0.001
Uric acid (mg/dl)	4.82 ± 1.08	5.08 ± 1.63	5.37 ± 1.58	0.032
Urinary microalbumin (mg / l)	9.34 ± 5.38	11.45 ± 4.80	41.36 ± 2.85	0.0001
Albumin / Creatinine ratio (mg / mmol)	0.99 ± 0.57	1.20 ± 0.52	2.37 ± 1.77	<0.0001

BUN-Blood Urea Nitrogen

P value <0.05 is considered statistically significant.

P value <0.0001 is considered highly statistically significant.

Statistically significant difference was observed in uric acid and serum creatinine levels. A highly significant difference was observed in urinary microalbumin and Alb/ Creat ratio. There is no statistical significant difference in BUN across the groups.

Table 5: Multiple comparative study showing the significant relationship of the biochemical parameters between the 3 groups

Parameters	Group I & II (n =138,61) p value	Group II & III (n=61,56) p value	Group I& III (n=138,56) p value
Serum Creatinine (mg/ dl)	0.0407	0.6508	0.0018
Uric acid (mg/ dl)	0.4646	0.4689	0.0296
Urinary microalbumin (mg / l)	0.8024	0.0001	<0.0001
Albumin/Creatinine ratio mg/mmol)	0.382	0.0001	<0.0001

P value <0.05 is considered statistically significant.

P value <0.0001 is considered highly statistically significant.

Considering the renal profile, statistical difference was observed in uric acid levels between group I & III Serum creatinine was found to be statistically significant between group I & II and group I & III. Urinary microalbumin and Alb/ Creat ratio showed highly statistical difference between group II & III and group I & III.

The microalbumin levels of individual groups were compared with the other variables to find out the correlation between them and the results are expressed as given in the following table.(Table 6)

Table 6 : Pearson correlation of Urinary microalbumin and other variables

Correlation of Urinary Microalbumin with other parameters	Group I		Group II		Group III	
	r value	P value	r value	P value	r value	P value
Microalbumin with SBP	-0.085	0.321	0.169	0.192	0.289	0.031
Microalbumin with DBP	0.010	0.907	-0.036	0.784	0.165	0.224
Microalbumin with BMI	0.041	0.632	0.023	0.861	0.023	0.866
Microalbumin with BUN	0.214	0.012	0.302	0.018	0.164	0.226
Microalbumin with Uric acid	-0.010	0.905	0.034	0.794	-0.018	0.898
Microalbumin with serum creatinine	0.131	0.125	0.073	0.576	-0.084	0.537
Microalbumin with Albumin /Creatinine Ratio	0.5235	<0.0001	0.216	0.094	0.83	<0.0001

P value <0.05 is considered statistically significant.

P value <0.0001 is considered highly statistically significant.

In group I and group II correlation was observed in microalbumin levels and BUN levels . A strong correlation was observed between Systolic blood pressure and microalbumin levels in hypertensives with end organ damage (Group III) . Microalbumin and urea levels showed a positive correlation in hypertensives without end organ damage. Highly significant correlation was observed between urinary microalbumin level in all the groups.

IV. Discussion

Albumin is a small and globular protein possessing negative charge at blood pH of 7.4. These negative charges in the albumin repel against the positive charges of the Glomerular Basement membrane thus

decreasing the filtration. In patients with microalbuminuria due to the loss of negative charges in Glomerular Basement Membrane the filtration of albumin is increased.

Normal urine contains up to 30 mg/g creatinine, or 30 mg albumin/L urine. [6] Increased urinary albumin excretion (UAE) has been suggested as a useful marker of end organ damage (EOD) as well as increased risk of cardiovascular disorders [7] .

In non-diabetic hypertensives the pathogenic mechanisms underlying increased UAE has not been elucidated. At present two mechanisms are found to play a role. [8, 9]

One mechanism suggests that there is an increased glomerular basement membrane permeability leading to elevated BP in the glomeruli. In glomeruli , blood enters through afferent arteriole and exits through efferent arteriole ,hence leakage of albumin in urine indicates damage to the blood vessel. The same type of damage can be present in other parts of the body[10] .Other mechanism suggests that this could also be due to early endothelial dysfunction of the blood vessels.[11, 12]

The association between Microalbuminuria (MA) and Hypertension has been studied as early as in 1974 by Parving et al [13]. MA has a major impact on cardio vascular risk [14]. It has become a prognostic marker for cardiovascular disorders.Thus several mechanisms like increased filtration, abnormalities of the glomerular basement membrane and endothelial dysfunction are responsible for an increase in trans glomerular passage of albumin in patients with essential hypertension [15]. Microalbuminuria is considered to be a marker of endothelial dysfunction and end organ damage.[16,17].

The prevalence of MA was found to be 33.3% according to Ravjit Kaur Sabharwal et al [18] in agreement with the study of Rosa TT, Cerasola G and Agrawal B [19,20,21] According to our study individuals in Group III the prevalence of microalbuminuria is (71.42 %) , higher than the findings obtained by the other studies [22,23,24]. MAGIC Study (Microalbuminuria – A Genoa Investigation on Complications) conducted by Roberto Pontremoli et al has indicated reported the prevalence of MA in essential hypertension as 6.67 %.. [25].

Several studies suggest that prevalence of MA in HT varies from 7 to 40 % depending upon the age and ethnic group[26,27,28,29,30]. However the prevalence was found to be 63% out of 100 hypertensives in a study by Sharan Badiger et al in 2011[31] Microalbuminuria represents the generalized vascular endothelial dysfunction thus contributing to increased cardiovascular disease risk [32]. Microalbumin starts increasing in hypertensives even before they go in for end organ damage.

In obesity there occurs an alteration in the vascular endothelial structure and function. This is found to predispose to peripheral and coronary artery disease . According to the Framingham Cohort study obesity accounts for 78% & 65% of Essential Hypertension in men and women. There is statistically significant difference in weight (p value 0.0001) and BMI (p value 0.0006) as the disease advances to hypertension with end organ damage. But there is no statistical difference between normal individuals when compared against hypertensives with no evidence of end organ damage Several epidemiological studies show that MA is an independent predictor of cardiovascular morbidity and mortality in patients with essential hypertension [33, 34]. Serum creatinine urea, uric acid (although in normal range) were significantly higher in hypertensives compared to the control group in a study conducted by Jalal et al in 2001[35] . In accordance with this study we observed a statistical difference in BUN, uric acid levels when hypertensives with end organ damage were compared against controls . Serum creatinine was found to be statistically significant between the groups showing that there is continuous increase in creatinine with the progression of the disease.

The spot urine Albumin Creatinine (A:C) ratio is a better estimate of 24 hrs Albumin Excretion Rate (AER) in urine [36,37,38]. Highly statistically significant difference (p< 0.0001) was observed in Albumin Creatinine ratio as the disease progresses from hypertension to hypertension with end organ damage in our study. As per the ADA 2001 recommendations [39], A: C ratio can be used for urinary albumin estimation to detect microalbuminuria.

There is no statistical significant increase in BUN across the groups probably due to

- (i) Easily dialysable property of urea as compared to creatinine
- (ii) Decreased intake of protein
- (iii) Decreased reabsorption of urea as the disease condition progresses.

However BUN showed a significant correlation with microalbumin in group I and group II (p =0.012 and p= 0.018) in a study conducted in the Egyptian population respectively as supported by the above study (p < 0.001) [40] . There is correlation between SBP and microalbumin only in hypertensives with end organ damage indicating that SBP increases significantly as the hypertensives reach the stage of getting end organ damage. BUN is correlated with microalbumin in group I & II and not in group III indicating that elevation of BUN levels onsets in hypertensives even before they go in for end organ damage. Microalbumin is correlated with urine creatinine indicating that microalbumin starts increasing in control group itself and remains elevated in hypertensives without evidence of end organ damage as well as with evidence of end organ damage. The

systemic capillary permeability is altered in hypertension due to acceleration of hyperfiltration, transcapillary macromolecular transport causing damage to endothelial cell membrane passage [41].

V. Conclusion

Essential hypertension is asymptomatic contributing to about 95% of hypertension. Essential hypertensives are unaware of the end organ damage. Various studies have suggested detection of microalbuminuria and determination of A:C ratio would provide an index of EOD in essential hypertensives. There has recently been considerable interest in the quantitative measurement of microalbumin to detect subtle effects of hypertension on the kidney. Considering the renal profile statistical difference, microalbumin is associated with endothelial dysfunction which is the hallmark of hypertension. Hence monitoring the microalbumin levels , A:C ratio in newly diagnosed as well as known hypertensives under control would help to assess the onset of end organ damage.

List of abbreviations

A: C

Albumin Creatinine ratio

BMI

Body Mass Index

BUN

Blood Urea Nitrogen

DBP

Diastolic Blood Pressure

MA

Microalbuminuria

SBP

Systolic Blood Pressure

Declarations

Competing interests

The authors declare that they have no competing interest.

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