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UACR: A novel risk marker for early detection of Atherosclerotic cardiovascular disease

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Abstract

Background: Hypertension is leading and modifiable risk factor for cardiovascular diseases and all-cause mortality. Left ventricular hypertrophy, seen in hypertensive patients is a strong predictor of unfavourable cardiovascular events. Microalbuminuria is considered as principal predictor of cardiovascular complications and mortality. Our study aims at finding prevalence of increased urine albumin creatinine ratio and left ventricular mass index in newly diagnosed hypertensive patients and finding a correlation among them.

Methodology: A hospital based cross sectional study was done. Adult patients visiting hospital OPD were screened for primary hypertension as per AHA (2017) guidelines and 40 were included in study. All patients underwent relevant blood and urine investigations. Urine albumin creatinine ratio was calculated in spot urine sample and left ventricular mass index was calculated using 2-D echocardiography.

Result: This study demonstrated that 70% newly diagnosed hypertensive patients had raised urine albumin creatinine ratio and 75% had raised left ventricular mass index. The data was plotted on scatter plot, which depicted the correlation between LVMI (g/m^2) and UACR (mg/g). Non-parametric tests (Spearman Correlation) were used to explore the correlation between the two variables and strong positive correlation was found between LVMI (g/m^2) and UACR (mg/g), and this correlation was statistically significant ($\rho = 0.74$, $p = <0.001$). It has been found that for every 1 unit increase in LVMI (g/m^2), the UACR (mg/g) increases by 2.58 units. Conversely, for every 1 unit increase in UACR (mg/g), the LVMI (g/m^2) increases by 0.05 units.

Conclusion: This study demonstrated the presence of microalbuminuria and evidence of left ventricular hypertrophy in a significant number of newly detected and untreated patients of essential hypertension. Also, there is significant association between LVMI and UACR (microalbuminuria) in hypertensive patients. Hence, we can recommend microalbuminuria as a screening tool for Left Ventricular Hypertrophy in newly diagnosed hypertensive patients so as to detect risk for cardiovascular events early and select our treatment strategy accordingly.

Keywords: Atherosclerotic cardiovascular disease (ASCVD); UACR; Left Ventricular Hypertrophy; Echocardiography; Early cardiovascular events; Microalbuminuria

1. Introduction

Hypertension is the leading but preventable risk factor for cardiovascular disease and all-cause mortality worldwide. As per AHA 2017, Hypertension is defined as SBP of more than or equal to 130 mm Hg or DBP of more than or equal to 80 mm Hg [1]. Over the last 4 decades, the prevalence of hypertension has increased especially in middle-income

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countries. However, due to the widespread use of anti-hypertensive agents, global mean blood pressure has remained constant or has decreased slightly [2].

From 1990 to 2019, people with hypertension in the age group of 30-79 years doubled, from 331 million women and 317 million men in 1990 to 626 million women and 652 million men in 2019[3].

Hypertension when uncontrolled leads to various end organ damages including coronary heart disease, heart failure, proteinuria, renal failure, vascular and hemorrhagic stroke, retinopathy, and chronic kidney disease.

Hypertensive heart disease includes various functional and structural changes in the heart secondary to hypertension. It has a spectrum of presentation from asymptomatic to angina pectoris, dyspnea, life-threatening arrhythmias, heart failure, and sudden cardiac death. Symptoms of hypertensive heart disease are attributable to reduced coronary reserve and impaired systolic and diastolic function of the left ventricle. The development of left ventricular hypertrophy is the most important factor in determining various presentations of hypertensive heart disease [4].

Sustained uncontrolled hypertension eventually results in chronic renal disease which remains asymptomatic during its progression. Hypertension damages renal vasculature and its pathogenetic determinants are (1) systemic blood pressure load, (2) degree to which such pressure is transmitted to the renal vascular bed, and (3) local tissue susceptibility to any given degree of barotrauma [5].

Diabetes is the leader followed by hypertensive nephrosclerosis as the second most common cause of end-stage renal disease. Hypertensive kidney disease involves afferent arteriole, glomeruli, and the renin-angiotensin system. It also injures tubular cells, leading to epithelial-mesenchymal transition and later tubulointerstitial fibrosis.[6]

Injury primarily determined at the glomerular level by hypertension causes changes in post-glomerular peritubular capillaries that in turn induce endothelial damage and hypoxia. Microvasculature dysfunction by inducing a hypoxic environment triggers inflammation, EMT with epithelial cells dedifferentiation, and fibrosis. Hypertensive kidney disease also includes podocyte effacement and loss, leading to disruption of the filtration barrier. [6,7,8]

Urinary albumin to creatinine ratio is a quantitative method of measuring microalbuminuria which refers to abnormally increased excretion rate of albumin in urine ranging from 30-299mg/g of creatinine. Microalbuminuria does not refer to small or abnormal albumin particles rather it is a small but abnormal increase in urinary albumin excretion. It is a marker of endothelial dysfunction. Albuminuria including microalbuminuria is associated with an increased risk of cardiovascular morbidity and mortality. In hypertensive patients, it is an early marker of renal disease and cardiovascular morbidity [9].

2. Material and methods

This was a hospital based cross-sectional study conducted in Department of Medicine, Lady Hardinge Medical College and Associated Hospitals, New Delhi, India.

All adult patients aged 18 years or older, presenting to OPD/Emergency or admitted to the medicine ward of Lady Hardinge Medical Colleges and Associated Hospitals with newly diagnosed Hypertension as per ACC/AHA hypertension guidelines [1] were included in this study.

2.1. Inclusion Criteria

Age \geq 18 years, newly diagnosed hypertension, and treatment naïve hypertension

2.2. Exclusion Criteria

Patients on regular antihypertensive medications, Diabetes mellitus, diagnosed secondary hypertension, Pregnant women, on steroid therapy, known cases of autoimmune diseases, and known structural (congenital/acquired/ischemic) heart disease.

After taking informed consent patients were subjected to a detailed history, examination, and following investigations (Hemogram, Liver function test, Kidney function test, S. Electrolytes, S. lipid profile, Thyroid function test, Fasting blood sugar, HbA1c, UACR, ECG, 2D – ECHO).

Blood pressure (BP) was measured using a manual aneroid sphygmomanometer using the auscultatory method. Patients were made to relax, sitting in a chair (feet resting on the floor, back supported) for >5min with the arm supported and appropriate size cuff on the patient's upper arm at the level of the right atrium, with no caffeine, exercise, and smoking for at least 30 min before measurement. BP was recorded in both arms and arm with higher reading was taken for subsequent readings. An average of 2 readings 2 minutes apart were taken as an individual's BP.

Microalbuminuria is UACR (urine albumin (mg/dl) to creatinine (g/dl) ratio) in the spot urine sample of 30-300mg/g and was measured using Beckman Coulter AU 680 in the spot urine sample.

Left ventricular mass index was calculated using hand-held 2D-Echocardiogram machine by the following formula developed by Devereux *et al.*:^[10]

$$\text{LVM} = 0.80 \times (1.04[\text{IVST} + \text{PWT} + \text{LVID}]^3 - \text{LVID}^2) + 0.6 \text{ g}$$

Here,

IVST is the interventricular septal thickness,

PWT is the posterior wall thickness,

LVID is the left ventricular internal diameter,

1.04 = specific gravity of the myocardium and 0.8 is the correction factor^[28].

LVM index (LVMI) was calculated by dividing LVM by the body surface area of the patients and represented as g/m². LVH was considered to be present when LVMI was ≥102 g/m² in men and LVMI ≥ 88 g/m² in women^[11,12].

2.3. Statistical Analysis

The observations and data were compiled, tabulated, and analyzed statistically using the MS EXCEL spreadsheet, and analysis was done using the latest available version of SPSS software. For continuous data mean, median, and standard deviation were calculated and for categorical data frequency and proportion were calculated. Data was represented in graphical form using histograms, pie charts, and scatter plots, and relevant parametric and non-parametric tests were applied. P-value of <0.05 was considered statistically significant. Non-parametric tests (Spearman Correlation) were used to explore the correlation between the two variables, as at least one of the variables was not normally distributed. When the variable was not normally distributed in the 2 subgroups, we used non-parametric tests (Wilcoxon-Mann-Whitney U Test) to make group comparisons.

3. Results

The mean (SD) of Age (years) was 50.15 (11.74). Most of the patients (57.5%) included in the study had age 41-60 years. 45.0% of the participants were male and 55.0% of the participants female.

The mean (SD) of UACR (mg/g) was 80.4 (103). 30.0% of the participants had UACR<30 mg/g and 70.0% of the participants had UACR≥30mg/g.

Non-parametric tests (Spearman Correlation) were used to explore the correlation between the two variables, SBP and UACR. There was a moderate positive correlation between Systolic BP (mmHg) and UACR (mg/g), and this correlation was statistically significant ($\rho = 0.47$, $p = 0.002$). For every 1 unit increase in Systolic BP (mmHg), the UACR (mg/g) increases by 2.24 units. Conversely, for every 1 unit increase in UACR (mg/g), the Systolic BP (mmHg) increases by 0.02 units. However, when SBP was compared in 2 groups of UACR i.e. UACR <30 mg/g vs UACR ≥30mg/g, mean (SD) of Systolic BP (mmHg) in the UACR<30 mg/g group and UACR ≥30mg/g group is 158.00 (18.19) and 170.21 (30.22). and this difference was not significant statistically ($W = 129.500$, $p = 0.257$).

There was no statistically significant correlation between Diastolic BP (mmHg) and UACR (mg/g) ($\rho = 0.24$, $p = 0.131$).

25.0% of the participants had normal LVMI and 75.0% of the participants had raised LVMI. The mean (SD) of LVMI (g/m²) in the males was 139.06 (34.86). The mean (SD) of LVMI females was 104.98 (29.58).

There was a strong positive correlation between LVMI (g/m²) and UACR (mg/g), and this correlation was statistically significant ($\rho = 0.74$, $p = <0.001$). For every 1 unit increase in UACR (mg/g), the LVMI (g/m²) increases by 0.05 units. Conversely, for every 1 unit increase in LVMI (g/m²), the UACR (mg/g) increases by 2.58 units.

Fisher's exact test was used to explore the association between 'UACR' and 'LVMI' and there was a significant difference between the various groups in terms of distribution of LVMI ($\chi^2 = 22.857$, $p = <0.001$). Strength of association between the two variables was high.

75.0% of the participants with normal UACR had no evidence of LVH on 2D-ECHO and 96.4% of the participants with raised UACR had raised LVMI i.e. LVH on 2D-ECHO.

Table 1 Correlation of UACR with other parameters

Parameters	UACR		p-value
	<30 mg/g (n = 12)	≥30mg/g (n = 28)	
Age (Years)	45.58 ± 6.93	52.11 ± 12.89	0.156 ¹
Gender			0.781 ³
Male	5 (41.7%)	13 (46.4%)	
Female	7 (58.3%)	15 (53.6%)	
Systolic BP (mmHg)	158.00 ± 18.19	170.21 ± 30.22	0.257 ¹
Diastolic BP (mmHg)	99.00 ± 8.76	101.07 ± 12.19	0.819 ¹
BMI (kg/m ²)	25.97 ± 4.65	26.56 ± 3.93	0.497 ¹
Total Cholesterol (mg/dL)	178.42 ± 41.94	177.37 ± 40.23	0.988 ¹
Triglycerides (mg/dL)	141.67 ± 45.36	151.66 ± 74.17	0.768 ¹
HDL (mg/dL)	47.25 ± 7.83	47.94 ± 14.71	0.535 ¹
LDL (mg/dL)	125.17 ± 37.65	120.31 ± 37.46	0.734 ¹
TSH (μIU/mL)	2.12 ± 1.07	2.33 ± 0.96	0.647 ¹
HbA1c (%)	5.51 ± 0.33	5.55 ± 0.44	0.700 ¹
LVMI (g/m ²) ***	87.39 ± 24.28	134.43 ± 30.71	<0.001 ¹
LVMI***			<0.001 ²
WNL	9 (75.0%)	1 (3.6%)	
High	3 (25.0%)	27 (96.4%)	

***Significant at $p < 0.05$, 1: Wilcoxon-Mann-Whitney U Test, 2: Fisher's Exact Test, 3: Chi-Squared Test

4. Discussion

4.1. Demography

A total of 40 patients were included in the study from hospital OPD, emergency, and medical wards. In this study, there were a total of 18 males and 22 females. The mean age of patients was 50.15 (± 11.74) years.

4.2. Blood Pressure

The mean (SD) of Systolic BP and diastolic BP was 166.55 (27.52) mm of Hg and 100.45 (11.20) mm of Hg, respectively. All patients included in the study had grade 2 hypertension as per AHA (2017).

4.3. BMI

In this study, 22.5 % of patients were overweight and 57.5% of patients were obese. Rest 20% of patients had normal BMI. The mean (SD) of BMI (kg/m²) was 26.38 (4.10).

(All patients were screened for diabetes mellitus using HbA1c and fasting blood sugar levels and none of the patients had thyroid dysfunction).

4.4. UACR

In my study, the mean (SD) of UACR (mg/g) was 80.4 (103). The urine albumin creatinine ratio was normal in 12 patients. However, the rest 28 patients i.e. 70% of patients had raised UACR. These results were compared with previous studies available.

The prevalence of microalbuminuria in hypertensive patients was reported to be 6%-42% in previous studies [13-18]. Maggon RR *et al* [18] conducted a study on 50 patients with essential hypertension and found a 44% prevalence of microalbuminuria. In our study prevalence of raised UACR was 70% which was higher compared to previous studies. Hypertension being a silent disease with not much of its clinical manifestations, higher average blood pressure, and long-standing undiagnosed hypertension could have been possible reasons for the same.

4.5. Correlations of UACR

4.5.1. Age, Gender, and BMI

In my study, the average age of normal UACR patients was 45.58 years and in patients with raised UACR, it was 52.11 years. However, this result was not statistically significant. This could have been due to the non-uniform distribution of patients among different age groups.

BMI and gender did not show any significant correlation with UACR.

Hitha *et al* conducted a study on 150 non-diabetic essential hypertensive patients in years 2005-2006 in Kerala, India, and found a direct correlation between age and microalbuminuria in their study. However, no significant correlation was established between gender with microalbuminuria and BMI with microalbuminuria. [19]

4.5.2. Blood pressure

We have found that urine albumin creatinine ratio was directly correlated with systolic blood pressure and this correlation was statistically significant. For every 1 mm of Hg increase in Systolic BP, the UACR (mg/g) increased by 2.24 units. However, UACR was not significantly correlated with diastolic blood pressure.

Poudel B *et al* conducted a study in 2012, in which 106 patients with essential hypertension and 106 normotensive patients were included. They studied the association between blood pressure and microalbuminuria and found a strong association of microalbuminuria with systolic and diastolic blood pressure, but no direct correlation was described. [20]

4.5.3. LVMI

In this study, the mean (SD) of LVMI was 120.31 (36.00) g/m². The mean (SD) of LVMI (g/m²) in the males was 139.06 (34.86) and in females was 104.98 (29.58). At the time of diagnosis, 75% of patients had left ventricular hypertrophy i.e. raised left ventricular mass index on 2D ECHO. A total of 30 out of 40 patients had LVH out of which 15 were males and 15 were females. Various studies had shown a different prevalence of LVH in untreated or newly diagnosed hypertension patients. Leoncini *et al* [21] conducted a study in 2002, which included 346 treatment-naive patients with primary hypertension and found LVH in 51% of patients and stated that patients with microalbuminuria were more likely to have LVH.

Hitha *et al* found a 29% prevalence of LVH in untreated hypertensive patients. [19]

However, the cutoff values taken for LVH in these studies were much higher than in our study. Also, there are few studies published (only 2) regarding the presence of LVH in newly diagnosed hypertension that has been conducted in India.

4.6. Correlation of LVMI and UACR

There was a strong positive correlation between LVMI (g/m²) and UACR (mg/g), and this correlation was statistically significant ($\rho = 0.74$, $p = <0.001$). The prevalence of LVH among patients with normal UACR and patients with raised UACR was 75.0% and 96.4% respectively. So, **almost all patients with raised UACR had evidence of LVH on 2D-**

ECHO. The mean value of LVMI in patients with normal UACR was 87.39 g/m² and in patients with raised UACR was 134.43 g/m². Also, it was found that for every 1 unit increase in UACR (mg/g), the LVMI (g/m²) increased by 0.05 units.

Plavnik *et al* conducted a study on 20 patients with primary hypertension, which also showed a significant correlation between urinary albumin excretion and LVMI.^[22]

Monfared A *et al* conducted a study on 110 patients with essential hypertension and found that patients with a higher urine albumin-creatinine ratio were more likely to have LVH.^[23]

5. Conclusion

The study demonstrated the presence of microalbuminuria and left ventricular hypertrophy in a significant number of newly diagnosed treatment naïve hypertensive patients. There is a significant positive correlation between systolic blood pressure and urine albumin creatinine ratio and between urine albumin creatinine ratio and left ventricular mass index in hypertensive patients. UACR is an economical investigation in resource-limited settings and it can be used as a surrogate marker for the development of left ventricular hypertrophy in hypertensive patients. Therefore, we recommend Urine albumin creatinine ratio as a baseline investigation in all patients with hypertension and Microalbuminuria as a screening tool for detecting left ventricular hypertrophy in newly diagnosed hypertensive patients in limited resource settings for appropriate intensive treatment strategy.

Compliance with ethical standards

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Disclosure of conflict of interest

We declare that there is no financial and personal conflict of interest.

Statement of ethical approval

An ethical committee approval has been obtained for the study.

Statement of informed consent

We declare that an Informed consent was obtained from all individual participants included in the study.

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