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Microalbuminuria in subclinical target organ damage and its correlation to creatinine clearance ratio in hypertension

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Abstract
Background: Urinary albumin excretion has been purported to be strongly linked to cardiovascular events in hypertensive patients. The prevalence of microalbuminuria in patients with essential hypertension and its relationship with target organ damage was evaluated with the present study, as the correlation of microalbuminuria and target organ damage except cardiovascular events has not been deliberated upon much in the past.
Objectives: To evaluate the relationship between microalbuminuria and reduced creatinine clearance with subclinical target organ damage in asymptomatic nondiabetic hypertensive patients.
Methodology: 120 hypertensive cases were studied from January 2019 to December 2020 in Dr VRK Womens Medical College, Hyderabad. Cases were evaluated for microalbuminuria, creatinine clearance, left ventricular hypertrophy and hypertensive retinopathy. Creatinine clearance was estimated by the Cockcroft-Gault formula. Left ventricular hypertrophy was determined by ECG and echocardiography. Retinal vascular changes were evaluated by direct ophthalmoscopy. Microalbuminuria was detected in 24 hours urine sample by immunoturbidimetric, assay.
Results: There was significant association between microalbuminuria (30%) and reduced creatinine clearance (38%) with target organ damage i.e. left ventricular hypertrophy [p < 0.002 & p 0.002 respectively] and hypertensive retinopathy [p 0.005 & p 0.03 respectively]. Patients with urine microalbumin had 30 times risk [95% CI: 3.6-253, p 0.001] and those with reduced creatinine clearance had 5.9 times the risk [95% CI: 1.7-19.4, p 0.0035] of developing target organ damage. But when present together the risk increased to 39.4 times [95% CI: 2.2-703, p 0.0124].
Conclusion: Results show that a reduction in creatinine clearance and/or presence of microalbuminuria is a marker of subclinical organ damage in patients with primary hypertension. Microalbuminuria showed better association with target organ damage than reduced creatinine clearance.

Keywords: Urinary albumin excretion, clearance, primary hypertension, subclinical, target organ damage

Introduction
Hypertension has long been recognized as a major health burden and particularly as a major risk factor for stroke, cardiovascular disease, end-stage renal disease, and overall mortality that affects all segments of the population [1]. Hypertension (HTN) particularly and significantly impacts healthcare systems in India [2, 3]. Hypertension, even in asymptomatic state, is related to different types of Target Organ Damage (TOD) and their clinical sequelae. Subtle TOD, such as Left Ventricular Hypertrophy (LVH), retinopathy, microalbuminuria and cognitive dysfunction occur early in the natural course of hypertensive disease; while catastrophic events such as stroke, heart attack, renal failure etc. are usually a result of long-standing uncontrolled hypertension. Majority of these patients have essential hypertension, defined as rise in blood pressure of unknown etiology.
Previously available robust data does indicate occurrence of proteinuria and Microalbuminuria (MA) (i.e. urinary albumin excretion rate of 20-200 mg/min or 30-300 mg/24 hr. or urinary albumin to creatinine ratio in the first voided sample in the morning greater than 30-300 mg/gm or early morning urinary albumin concentration of 20-200 mg/L) in hypertensive adults to be independent predictors of Cardiovascular (CV) morbidity and mortality [4-6]. Infact, MA is the earliest marker of hypertensive (and diabetic) nephropathy.

Further, MA has been shown to be reversible with optimal blood pressure and blood sugar control, at least in early stages [7, 8]. The prevalence of MA and its association with TOD among patients with essential hypertension has not been deliberated upon much by the researchers from this part of the world. The present study was hence planned with the objective of estimation of prevalence of microalbuminuria, assessment of probable risk factors for its development and the relationship of microalbuminuria to target organ damage amongst essential hypertension cases.

Objectives of the study

1. To find out the relationship of Microalbuminuria with subclinical target organ damage.
2. To study the pattern of microalbuminuria in patients of essential hypertension.
3. To find the relationship of Creatinine clearance and subclinical target organ damage

Material's and Methods

Patients admitted to Dr. VRK Womens Medical College from Jan 1, 2019 to Dec 31, 2020 with essential hypertension were chosen as subjects for the study considering the inclusion and exclusion criteria.

Number of study group: One

Study Design

120 Patients selected by random sampling procedure after matching for inclusion and exclusion criteria were included in the study. A pretested proforma was used to collect the relevant data. Follow up was done on inpatient admission and on outpatient department basis.

Ethical Committee Approval: The Ethical committee approval was obtained to carry out the study in the hospital.

Inclusion criteria

Patients admitted to this hospital within the study period, who had been previously diagnosed with essential hypertension according to JNC VII criteria –

a. Hypertension Stage 1: Systolic140 to 159 mm Hg and diastolic 90 to 99 mmHg.

Stage 2: Systolic > 160 mm Hg or diastolic > 100 mm Hg.

b. Past history of essential hypertension.
c. Age group of 30 - 60 years

Exclusion criteria

- Previously diagnosed cases of secondary hypertension,
- Pregnant women,
- Diabetes mellitus,
- Urinary tract infections,
- Renal disease (Serum Creatinine > 1.4 mg/dl for females and > 1.5 mg/dl for men),
- Presence of overt proteinuria [>300mg/d of albuminuria]
- Chronic heart failure (NYHA classes III and IV),
- Positive history or clinical signs of ischemic heart disease and cerebrovascular disease.
- Severe obesity (defined as body weight >150% of the ideal body weight or BMI > 40),
- Underweight (defined as BMI< 18.5)
- Disabling diseases such as dementia or inability to co-operate.
- Patients already on angiotensin converting enzyme inhibitor drugs.

Based on the level of BP, the patients were divided into three groups as follows

Less than 140/90 mm Hg. (Adequate control with drug therapy

- Systolic BP: 140 - 159 mm Hg

Diastolic BP: 90 - 99 mm Hg - Stage 1 of JNC 7 report

- Systolic BP: > 160 mm Hg

Diastolic BP: > 100 mm Hg - Stage 2 of JNC 7 report

BP was recorded in the arms with Mercury Sphygmomanometer, two recordings during the IP treatment period & on each occasion, two readings were taken with the patient sitting relaxed, back supported, for five minutes and arm supported at the level of heart.

Body mass index: Weight and height was measured for all ambulant patients and BMI expressed in kg/m^2. Based on BMI, the study group was classified into:

- Normal: 18.5 - 24.9
- Over weight: 25.0 - 29.9
- Moderately Obese: 30 - 34.9
- Severely Obese: 35 – 39.9
- Extremes of weight i.e. Morbid obesity (BMI >40) and underweight (BMI< 18.5) were excluded as per exclusion criteria to avoid errors during the calculation of CCR.

1. Examination of all organ systems were done
2. Fundus Examination: Done by direct ophthalmoscopy; pupilary dilatation achieved using 1% Tropicamide. According to Fundus findings, the patients were divided into 5 groups. (Refer to Review of Literature):

a. Fundus normal
b. Gr I Hypertensive Retinopathy
c. Gr. II Hypertensive Retinopathy
d. Gr. III & IV Hypertensive Retinopathy

Investigations done included

Random blood sugar was done in all patients to exclude diabetes.

1. Serum creatinine: Only those patients with in normal limit (Serum Creatinine < 1.4 mg/dl for females and <1.5 mg/dl for males) were taken up for the study. Serum creatinine was measured using Jaffe Colorimetric method on a Roche Hitachi 912 analyzer.
2. Creatinine clearance was estimated by means of the serum creatinine level using the Cockcroft-Gault formula. This value was adjusted for body surface area (BSA). A creatinine clearance of less than 60ml/min/1.73m^2 was considered as reduced.
3. Microalbuminuria: It was done using the Erba-Mannheim urinary albumin assay - an immunoturbidimetric, *in vitro* diagnostic assay for quantification of albumin in human urine by means of clinical chemistry analyzer. This method is done by

measurement of antigen-antibody reaction by the end-point method. The method is sensitive to very low concentrations of urinary albumin. The following instructions were given 24 - hour urine sample collection -

a. On day 1,urinate into the toilet upon arising in the morning
b. Collected all subsequent urine (in a special container) for the next 24 hours.
c. On day 2, urinate into the container in the morning upon arising
d. Cap the container, label the container with patient name, the date, the time of completion, and return it as instructed

The patients were asked to avoid exercise or exertion prior to urine collection. In women, urine was collected during the non menstrual phase of their cycles

A value of 30-300 mg/d of albuminuria was considered as microalbuminuria

4. A Mild renal dysfunction was defined as presence of urine albumin >30mg/d and/or a creatinine clearance < 60 ml/min/1.73m^2 as per KDGIO 2012 guidliness.
5. Target organ damage (TOD) was defined as the presence of LVH or Retinopathy or both

Results

In the present study, a total of 120 patients with essential hypertension were studied from Jan 1, 2019 to Dec 31, 2020 in Dr. VRK Women's Medical College after considering the inclusion and exclusion criteria.

Table 1: General Characteristics of the Study Population

Parameters	Study group (Mean ± SD)
Age (years)	50.16 ± 8.84
Duration of hypertension (years)	6.69 ± 4.898
Systolic BP (mm/Hg)	158.74 ± 21.78
Diastolic BP (mm/Hg)	94.38 ± 11.80
RBS (mg/dl)	98.406 ± 20.28
Total Cholesterol (mg/dl)	195.1 ± 48.816
24 hour Urine albumin (mg/d)	37.23 ± 41.808
Serum creatinine (mg/dl)	0.951 ± 0.220
Creatinine Clearance (ml/min)	79.59 ± 26.23

Table 2: Age Distribution of the Study Group

Age in years	No. of patients	Percentage
30- 40	26	21.6%
41-50	30	25%
51-60	64	53.3%

Table 3: Sex Distribution of the Study Group

Sex	No. of patients	Percentage
Male	64	53.3%
Female	56	46.7%

Table 4: Percentage of Microalbuminuria

	No. of patients	Percentage
Microalbuminuria	36	30%
Normoalbuminuria	84	70%

Table 5: Percentage of Reduced Creatinine Clearance

	No. of patients	Percentage
CCR < 60 ml/min	46	38%
CCR > 6o ml/min	74	62%

Table 6: General characteristics of Microalbuminuria and Reduced creatinine Clearance Groups

Parameters	Microalbuminuria (>30mg/d)		't' value	'p' value	Creatinine clearance (< 60 ml/min)		't' value	'p' value
	Present	Absent			Present	Absent		
Age (years)	53.90 ± 5.604	48.56 ± 9.509	2.218	0.032	53.53 ± 6.474	48.06 ± 9.508	2.428	0.019
Duration (years)	10.40 ± 5.067	5.11 ± 3.907	4.393	0.000	10.10 ± 5.188	4.58 ± 3.297	5.050	0.000
Systolic BP (mm/Hg)	170.79 ± 22.67	153.6 ± 19.46	2.988	0.005	165.7 ± 19.925	154.5 ± 22.027	1.989	0.053
Diastolic BP (mm/Hg)	101.8 ± 12.018	91.20 ± 10.285	3.474	0.002	97.58 ± 11.802	92.58 ± 11.498	1.683	0.099
RBS (mg/dl)	91.41 ± 18.024	101.5 ± 20.642	1.784	0.09	92.58 ± 19.636	102.03 ± 20.08	1.789	0.080
Sr creatinine (mg/dl)	1.140 ± 0.1502	0.870 ± 0.195	5.248	0.000	1.131 ± 0.839	0.839 ± 0.1786	6.563	0.000
Creatinine Clearance (ml/min)	60.55 ± 13.247	87.76 ± 26.26	4.162	0.000	54.49 ± 4.299	95.20 ± 21.526	8.942	0.000
24 hrs Urine albumin (mg/d)	92.93± 35.736	13.36 ± 6.316	14.08	0.000	64.34 ± 50.727	20.38 ± 23.033	4.584	0.000
Total Cholesterol (mg/dl)	220.0 ± 70.723	184.2 ± 31.013	2.248	0.009	198.7 ± 34.467	192.6 ± 56.254	0.473	0.640

In the study it was observed that patients with microalbuminuria had a statistically significant increase in age, duration of hypertension, systolic and diastolic BP, total cholesterol, Sr creatinine and reduced creatinine clearance when compared to patients who were normoalbuminuric.

In patients who had a reduced creatinine clearance (< 60 ml/min/1.7m^2) there was a statistically significant increase in age, duration of hypertension, Sr creatinine and 24 hr urine albumin when compared to patients who a creatinine clearance >60 ml/min/1.7m^2. But, although there was a increase in systolic BP, diastolic BP and total cholesterol in patients with reduced creatinine clearance they were found to be not statistically significant (p > 0.05).There was no significant association of RBS with either groups.

Table 7: Distribution of Microalbuminuria and Creatinine Clearance among Males and Females

Sex	Total no	Microalbuminuria				Creatinine clearance			
		Present		Absent		<60 ml/min		>60 ml/min	
		No	%	No	%	No	%	No	%
Male	64	18	28.1%	46	71.9%	18	28.1%	46	71.9%
Female	56	18	32.1%	38	67.9%	28	50%	28	50%

There was no statistically significant difference between male and female hypertensive cases for microalbuminuria or reduced creatinine clearance.

Table 8: Distribution of Microalbuminuria and Creatinine Clearance depending upon the duration of hypertension

Duration of Hypertension (yrs)	Total no	Microalbuminuria				Creatinine clearance			
		Present		Absent		<60 ml/min		>60 ml/min	
		No	%	No	%	No	%	No	%
<5	58	6	10.3%	52	89.7%	10	17.2%	48	82.8%
6-10	36	14	38.9%	22	61.1%	16	44.4%	20	55.6%
11-15	16	8	50%	8	50%	10	62.5%	6	37.5%
>16	10	8	80%	2	20%	10	100%	0	0%

Table 9: Distribution of Microalbuminuria and Creatinine Clearance among Different Age Groups

Age (yrs)	Total no	Microalbuminuria				Creatinine clearance			
		Present		Absent		<60 ml/min		>60 ml/min	
		No	%	No	%	No	%	No	%
30-40	26	0	0%	26	100%	2	7.6%	24	92.3%
41-50	30	12	40%	18	60%	12	40%	18	60%
51-60	64	24	37.5%	40	62.5%	32	50%	32	50%

It was observed that as the age advances, the proportion of microalbuminuria (p 0.04) and reduction in creatinine clearance (p 0.03) increased among these hypertensive patients and the difference was statistically significant.

Table 10: Body Mass Index with Microalbuminuria and Creatinine Clearance

BMI*	Total no	Microalbuminuria				Creatinine clearance			
		Present		Absent		<60 ml/min		>60 ml/min	
		No	%	No	%	No	%	No	%
Normal	60	14	38%	46	54%	22	47%	38	51%
Over weight	38	20	55%	18	21%	16	34%	22	29%
Moderately Obese	18	2	5.6%	16	19%	6	13%	12	16%
Severely Obese	4	0	0%	4	100%	2	50%	2	50%

***** Both underweight (BMI< 18.5) and morbid obesity (BMI> 40) groups were excluded so that there were no errors in calculation of Creatinine Clearance

There was statistically significant association observed between BMI and microalbuminuria (p 0.05) but not with reduced creatinine clearance. (p > 0.949).

Table 11: Lipid Profile with Microalbuminuria and Creatinine clearance

Lipid profile	Total no	Microalbuminuria				Creatinine clearance			
		Present		Absent		<60 ml/min		>60 ml/min	
		No	%	No	%	No	%	No	%
Favourable	66	8	12.1%	58	87.8%	10	15.1%	56	84.8%
Unfavourable	54	28	51.8%	26	48.1%	34	62.9%	20	37%

Both microalbuminuria and reduced creatinine clearance were associated with an unfavourable lipid profile in a statistically significant manner ($p < 0.002$).

Table 12: Microalbuminuria, Creatinine Clearance and the Level of Blood Pressure

Stage of hypertension	Total no	Microalbuminuria				Creatinine clearance			
		Present		Absent		<60 ml/min		>60 ml/min	
		No	%	No	%	No	%	No	%
Normal	18	2	11.1%	16	89.9%	4	22.2%	14	77.8%
Stage 1	36	2	5.6%	34	94.4%	10	27.8%	26	72.2%
Stage 2	66	32	48.5%	34	51.5%	32	48.5%	34	51.5%

The percentage of patients with microalbuminuria increased with severity of hypertension i.e. the quantity of microalbuminuria was more in patients with stage II hypertension as compared to stage I hypertension, which was statistically significant (p0.003). Also, although the patients with higher BP had an increased proportion of reduced creatinine clearance, they were found to be statistically insignificant (p 0.195).

Table 13: LVH with Microalbuminuria and Creatinine Clearance

Left Ventricular Hypertrophy	Total no	Microalbuminuria				Creatinine clearance			
		Present		Absent		<60 ml/min		>60 ml/min	
		No	%	No	%	No	%	No	%
Present	42	30	71.4%	12	28.6	28	66.7%	14	33.3%
Absent	78	6	7.7%	72	92.3%	18	23.1%	60	76.9%

In the present study, 42 patients were found to have left ventricular hypertrophy. Of these, 30 patients (71.4%) had the presence of microalbuminuria when compared with 12 (28.6%) who did not have microalbuminuria. Of the remaining 78 cases who had no LVH, only 6 (7.7%) where positive for microalbuminuria while rest 72 cases (92.3%) were normoalbuminuric.

Out of the 42 patients in the study who had left ventricular hypertrophy, 28 cases (66.7%) had a CCR <60 ml/min/1.73m^2 as against only 14 cases (33.3%) who had a CCR > 60 ml/min/1.73m^2. In patients who had no left ventricular hypertrophy, only 18 (23.1%) had a CCR <60 ml/min/1.73m^2 while 60 (76.9%) had a CCR >60 ml/min/1.73m^2.

This shows that most number of cases having microalbuminuria (p <0.002) and a reduced creatinine clearance (p 0.002) were found to have LVH in these essential hypertensive cases, which is statistically significant.

Table 14: Target Organ Damage and microalbuminuria

Microalbuminuria	Total no	CCR < 60 ml/min		LVH		Retinopathy	
		No	%	No	%	No	%
Present	36	26	72%	30	83%	24	66%
Absent	84	20	23%	12	14%	20	23%

Reduced creatinine clearance (p<0.002), left ventricular hypertrophy (p<0.002), and retinopathy (p0.002) was significantly higher in patients with microalbuminuria.

Discussion

Microalbuminuria is frequently seen in patients with essential hypertension and is relatively well established as a predictor of a higher risk for cardiovascular and probably renal dysfunction and subsequent mortality. Due to lack of credible locally relevant evidence, the present study was undertaken to assess prevalence of Microalbuminuria (MA), probable risk factors for its development and the relationship of Microalbuminuria (MA) to Target Organ Damage (TOD) amongst patients of essential hypertension.

Microalbuminuria has gradually been confirmed to be a marker of CV risk in diabetic individuals [9-10]. Significance of its presence in essential hypertension cases is also getting obvious one study at a time. MA was reported to be associated with increasing age, increased duration and severity of hypertension, obesity and dyslipidemia; findings observed in this study are corroborating available evidence [11-13].

Left ventricular hypertrophy (94.28%) and stroke (92.3%) were observed significantly more commonly in those with MA and so were progressive retinopathy changes (72.54%). Retinopathy, LVH, stroke and dyslipidemia remained independently associated with of MA even after multivariate analysis. This implies significantly higher chances of development of macro- as well as microvascular complications amongst hypertensives with microalbuminuria than without it. Significant correlations between MA and TOD in the form of major ECG abnormalities and vascular retinal changes were also reported by Pontremoli *et al*., Hitha *et al*., observed similar correlation between presence of MA and higher incidence of stroke as well as retinopathy, further substantiating authors observations. The presence of MA is thought of as the renal manifestation of generalized increased endothelial dysfunction occurring as part of the disease process; which leads to the hypothesis that certain degree of correlation continuum exists between CV risk factors and the process from early to final renal damage [14].

Hypertension is a major public health problem in India and in other developing countries. Hypertension affects approximately 25% of the adult population worldwide and its prevalence is predicted to increase by 60% by 2025 A.D [15].

The present study included 60 cases of essential hypertension that met the inclusion and exclusion criteria. Out of these 60 cases, 18 cases were positive for microalbuminuria and 23 cases were found to have a reduced creatinine clearance (< 60ml/min/1.73m^2).

The percentage of microalbuminuria in essential hypertension cases in the present study was 30% as compared to percentage of microalbuminuria found in other studies ranging from 6.7% to 64%, like in studies conducted by Pontremoli (6.7%) [16].

The percentage of reduced creatinine clearance in present study was 38% as compared to other studies ranging from 10% to 33%, like in studies conducted by Cerasola G [17] (10%).

The mean age of 60 essential hypertensive cases in present study population was 50.15 ± 8.83 years.

The percentage of microalbuminuria was more in patients with advancing age when compared to normoalbuminuric patients (p 0.031). The observation in present study was also observed in studies by Hitha B [18].

The percentage of reduced creatinine clearance was found increasing with advancing age when compared to those with CCR > 60 ml/min (p 0.018). This finding correlated with findings G Cerasola *et al*. [17].

In this study, Reduced creatinine clearance was seen with a significant positive association with duration of hypertension (10.09 ± 5.187 yrs versus 4.57 ± 3.296yrs, p <0.001). Also, despite an increase in proportion of reduced eGFR with higher degrees of mean SBP (165.65 ± 19.924 mmHg VERSUS 154.43 ± 22.026 mmHg, p 0.052) and mean DBP (97.57 ± 11.801 mmHg VERSUS 92.57 ± 11.497 mmHg,p 0.098) they were found not to be significant.

Lipid profile of study group was stratified as favourable and unfavourable biased on the cut off ATP III guidelines of NCEP after individualising each patient on their risk factors. Mean Total Cholesterol was 194.9 ± 48.815 mg/dl in this study.

There was a significant increase in unfavourable lipid profile among cases who where microalbuminuric than

others (p<0.001).These findings were in concordance with findings of B. Hitha *et al*. [18] in a population of 150 hypertensive patients. In the MAGIC study involiving 787 hypertensive patients found significant correlation between ACR and HDL-C.

Mild renal dysfunction and target organ damage

Out of the total 120 patients, 56 patients had mild renal dysfunction (46%) and 64 patients had presence of TOD (53%).This study demonstrates that mild renal dysfunction is associated with subclinical end-organ damage namely, LVH and retinopathy, in a population with primary hypertension and normal serum creatinine levels. In fact patients with creatinine clearance < 60 mL/min and/or urine albumin > 30 mg/d showed significantly higher left ventricular mass index and retinopathy grades as compared with those with normal glomerular filtration rate and urinary albumin excretion.

Conclusion

1. Hypertension is a major community health problem usually associated with early target organ damage. Therefore, a thorough assessment of cardiovascular risk is a prerequisite for an effective management strategy in these patients.
2. In the present study urine microalbumin was found in 30% of cases and a reduced creatinine clearance in 38% of the cases.
3. Microalbuminuria was seen with more advancing age and duration of hypertension, with higher BP (both systolic and diastolic), higher BMI, an unfavourable lipid profile and a lower creatinine clearance.
4. Reduced creatinine clearance was associated with both increasing age and duration of hypertension, an unfavourable lipid profile and a higher urine albumin excretion.
5. Subclinical hypertensive target organ damage was present in 53% of the cases.

Hypertensive retinopathy was seen in 36% and LVH in 35% of the cases.

6. Both microalbuminuria and reduced creatinine clearance had significant association with target organ damage i.e. left ventricular hypertrophy and hypertensive retinopathy.
7. Presence of both microalbuminuria and creatinine clearance together had a synergistic effect in increasing the risk of organ damage than either one of them alone.
8. More extensive screening for microalbuminuria and reduced creatinine clearance should be performed in hypertensive subjects to facilitate better stratification of absolute cardiovascular risk, especially in elderly patients with hypertension of more than five years duration.

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Conflict of Interest

None

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