ISSN: 2395 - 0471

International Journal of Clinical and Biomedical Research

Original Article

MICROALBUMINURIA IN SUBCLINICAL TARGET ORGAN DAMAGE AND ITS CORRELATION TO CREATININE CLEARANCE RATIO IN HYPERTENSION

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Received: 20th June 2015, Accepted: 15th July 2015.

ABSTRACT

Background: Target organ damage takes place early in course of hypertension. But, despite this, the disease remains inadequately controlled in majority of patients partly because of its asymptomatic nature. With incidence of hypertension on the rise, there have not been adequate studies in our country linking hypertensive target organ damage with microalbuminuria and creatinine clearance especially in asymptomatic patients. **Aims:** To find the relationship between microalbuminuria and reduced creatinine clearance with subclinical target organ damage in asymptomatic primary hypertensive patients. **Material & Methods:** 60 hypertensive patients were evaluated for mild renal dysfunction defined as 24 hour urine albumin(UA) > 30 mg/d and/or Creatinine Clearance (CCR) < 60 ml/min/1.73m^2 .Target organ damage evaluated were retinopathy (direct fundoscopy) and Left ventricular hypertrophy (2D ECHO). **Results:** There was significant association between microalbuminuria (30 %) and reduced creatinine clearance (38%) with target organ damage i.e. left ventricular hypertrophy [p < 0.001 & p 0.001 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]. **Conclusions:** 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: Microalbuminuria, mild renal dysfunction, primary hypertension, subclinical, retinopathy, target organ damage.

INTRODUCTION

Hypertension is a major public health problem in India and in other developing countries. HTN is directly responsible for 57% of all stroke deaths and 24% of all coronary heart disease (CHD) deaths in India.[1] In India, the prevalence is 22% – 45% among men and about 16% – 38% among women.[2]

Target organ damage due to hypertension results in adverse prognostic significance irrespectively of whether it involves the structure and/or function of the heart, brain, kidney, or vessels.[3]Studies have shown when organ damage is present, patients usually have a high total cardiovascular (CV) risk [4] i.e., a chance of having a morbid or fatal CV event within 10 years >20%.

The kidney has a dual role in primary hypertension. On the one hand, it is the cause of elevated blood pressure and on the other it may suffer from the long-term negative consequences of the hypertensive state. As renal function has shown to be inversely related to the occurrence of cardiovascular events, it may serve as a sensor of cardiovascular risk. [5]

Mild renal dysfunction(UA > 30mg/d and/or CCR <60ml/min) is a common finding in patients with hypertension and is associated with an increased risk for cardiovascular events as well as progression to end-stage renal disease.[6,7] This cardiovascular risk, progressively increases as renal function declines.[8]

Therefore, assessment of these subclinical target-organ damage represents an important aspect for the risk stratification of these hypertensive patients. This has led to the emergence of the concept "Global cardiovascular risk". It is imperative that these changes of end organ damage be picked up early so as to identify patients who require more aggressive management. In this context, assessment of subclinical target organ damage has become a key aspect in evaluating and managing hypertensive patients.

MATERIALS AND METHODS

This was a case series study conducted in the department of internal medicine, S.Nijalingappa Medical College and HSK Hospital, Bagalkot, a tertiary care hospital. 60 subjects with a diagnosis of essential hypertension who were asymptomatic and aged between 30 – 60 years were included in the study from Jan 1, 2013 to Dec 31, 2013. Previously diagnosed cases of secondary hypertension, Pregnancy, 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, 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 were excluded from the study. Institutional ethical committee clearance was obtained for the study and all patients participating in this study had given their informed written consent .

A diagnosis of hypertension was confirmed from history. The duration of hypertension, treatment, history of smoking/ other habits, symptoms pertaining to cardiovascular, renal, peripheral vascular system, ocular and nervous system was meticulously asked for, which could suggest the possibly of a pre-existing target organ damage. BP was recorded with two readings taken with the patient sitting relaxed, back supported, for five minutes and arm supported at the level of heart. JNC 7 classification was used to stratify the severity of hypertension. All subjects underwent routine Blood and urinary examinations, 12 lead ECG, opthalmoscopic evaluation and 24 hour urinary albumin after a written consent. Subjects who had left ventricular hypertrophy (LVH) in ECG as per Sokolow - Lyon Index or the Romhilt - Estes point score system were confirmed with Two dimensional guided M-mode echocardiography. A Left ventricular mass index of more than 115 gms / m^2 in men and 95 gms / m^2 in women were taken as the levels, above which LVH was be diagnosed as per EHC 2013 guidelines. Subjects were taken as having LVH only if they were positive for both ECG and echocardiography. Hypertensive retinopathy was evaluated by direct ophthalmoscopy and classified by Keith - Wagener - Barker system. Creatinine clearance was estimated by 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. 24 hour urine albumin was estimated 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 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. Target organ damage (TOD) was defined as the presence of LVH or Retinopathy or both.

STATISTICAL ANALYSIS

Statistical analysis was done with SPSS software and OPEN EPI version 2.3.1 Chi-square test to study the relationship between microalbuminuria, creatinine clearance and other variables. P value was calculated for all the variables and a value less than 0.05 was considered significant. Unpaired Student 't' test was used to analyse quantitative data.

RESULTS

The mean age group of the subjects were 50.15 ± 8.83 years with an average duration of hypertension of 6.68 ± 4.89 years. The mean 24 hour urine albumin of the population was 37.22 mg/d and creatinine clearance 79.58 ml/min. Of the 60 cases, 18 cases

were positive for urine microalbumin (30 %) and 23 cases (38 %) had reduced creatinine clearance (Table 1).

Microalbuminuria showed a statistically significant increase with 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 had creatinine clearance >60 ml/min/1.7m^2. But, although there was increase in systolic BP, diastolic BP and total cholesterol in patients with reduced creatinine clearance they were found to be not statistically significant ($p > 0.05$).Both microalbuminuria and reduced creatinine clearance had a significant association with unfavourable lipid profile (<0.001).

Table 1. 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)	53.89 ± 5.603	48.55 ± 9.508	2.217	0.031	53.52 ± 6.473	48.05 ± 9.507	2.427	0.018
Duration (years)	10.39 ± 5.066	5.10 ± 3.906	4.392	0.000	10.09 ± 5.187	4.57 ± 3.296	5.049	0.000
Systolic BP (mm/Hg)	170.78 ± 22.66	153.5 ± 19.45	2.987	0.004	165.6 ± 19.924	154.4 ± 22.026	1.988	0.052
Diastolic BP (mm/Hg)	101.7 ± 12.017	91.19 ± 10.284	3.473	0.001	97.57 ± 11.801	92.57 ± 11.497	1.682	0.098
RBS (mg/dl)	91.40 ± 18.023	101.4 ± 20.641	1.783	0.08	92.57 ± 19.635	102.02 ± 20.07	1.788	0.079
Sr creatinine (mg/dl)	1.139 ± 0.1501	0.869 ± 0.194	5.247	0.000	1.130 ± 0.838	0.838 ± 0.1785	6.562	0.000
Creatinine Clearance (ml/min)	60.54 ± 13.246	87.75 ± 26.25	4.161	0.000	54.48 ± 4.298	95.19 ± 21.525	8.941	0.000
24 hrs Urine albumin (mg/d)	92.92 ± 35.735	13.35 ± 6.315	14.07	0.000	64.33 ± 50.726	20.37 ± 23.032	4.583	0.000
Total Cholesterol (mg/dl)	219.9 ± 70.722	184.1 ± 31.012	2.247	0.008	198.6 ± 34.466	192.5 ± 56.253	0.472	0.639

Table 2. Grades of Retinopathy in relation to Microalbuminuria and Creatinine Clearance

Grades of Retinopathy	Total no	Microalbuminuria				Creatinine clearance			
		Present		Absent		<60 ml/min		>60 ml/min	
		No	%	No	%	No	%	No	%
Normal	38	6	15.8%	32	84.2%	11	28.9%	27	71.1%
Grade 1	8	3	37.5%	5	62.5%	2	25%	6	75%
Grade 2	9	5	55.6%	4	44.4%	6	66.7%	3	33.3%
Grade 3 & 4*	5	4	80%	1	20%	4	80%	1	20%
Chi Square		**12.62**				**8.7**			
p-value		**0.005**				**0.03**			

*Stage 3 &4 are combined for statistical analysis

Out of the total 60 patients, 28 patients had mild renal dysfunction (46%) and 32 patients had presence of TOD (53%).

Retinopathy in this study was observed in 22 subjects (36.6%). But out of the 18 subjects who had urine microalbumin present, 12 subjects had the presence of hypertensive retinopathy (66%, p0.001). In 23 subjects with reduced creatinine clearance, retinopathy was found in 12 subjects (52%, p <0.049). Also, increasing severity of hypertensive retinopathy grades was associated with increasing incidence of microalbuminuria (p 0.005) and reduced creatinine clearance (p <0.03) (Table 2).

Left ventricular hypertrophy (LVH) detectable by both ECG and 2D ECHO was seen in 21 out of 60 patients (35%). Out of 18 Subjects with presence of urine microalbumin, 15 had LVH (83%, p<0.001). Again, 14 out of 23 subjects (60%, p <0.002) with reduced creatinine clearance had LVH. Of the remaining 39 cases who had no LVH, only 3 (7.7%) where positive for microalbuminuria and 9 (23.1%) had a creatinine clearance <60 ml/min/1.73m^2.

Reduced creatinine clearance (p<0.001), left ventricular hypertrophy (p<0.001), and retinopathy (p<0.001) was significantly higher in patients with microalbuminuria. Similarly, the proportion of microalbuminuria (p<0.001), left ventricular hypertrophy (p<0.002) and retinopathy (0.049) was found statistically significantly higher in patients with CCR<60 ml/min (Figures 1, 2 & 3).

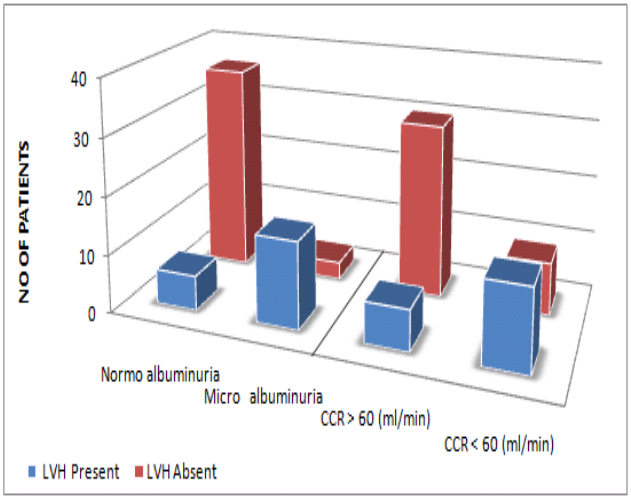

Figure 1. LVH with Microalbuminuria and Creatinine Clearance

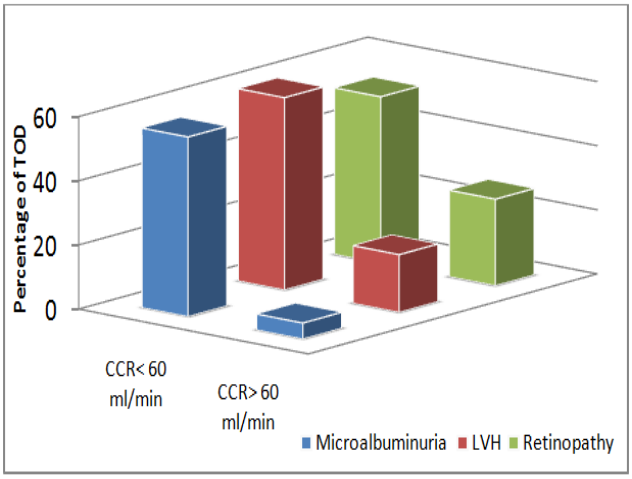

Figure 2. Target Organ Damage and Creatinine Clearance Rate

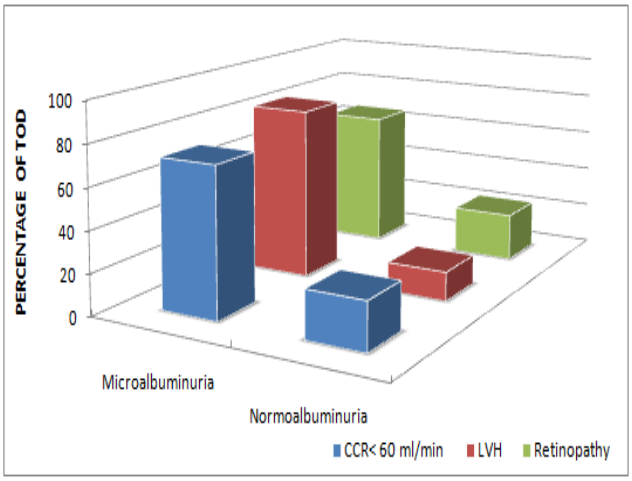

Figure 3. Target Organ Damage and microalbuminuria

A urine albumin level of more than 36 mg/day (p <0.001) was associated with increased incidence LVH (Figure 4) [Sensitivity–71.4(95% CI- 47.8 - 88.7), Specificity – 94.9 (95% CI- 82.7 - 99.4)] and more than 25 mg/day (p<0.0052) was associated with increased incidence retinopathy (Figure 5) [Sensitivity–59.1(95% CI- 36.4 - 79.3), Specificity – 84.2(95% CI- 68.7 - 94.0)].

A creatinine clearance of less than 63 ml/min (p<0.0023)was associated with increased incidence LVH (Figure 6) [Sensitivity–71.4 (95% CI- 47.8 - 88.7), Specificity – 76.9 (95% CI- 60.7 - 88.9)] and increased incidence of retinopathy (p 0.009) when creatinine clearance was less than 67.1 ml/min (Figure 7) [Sensitivity–68.2 (95% CI- 45.1 - 86.1), Specificity – 68.4 (95% CI- 51.3 - 82.5)].

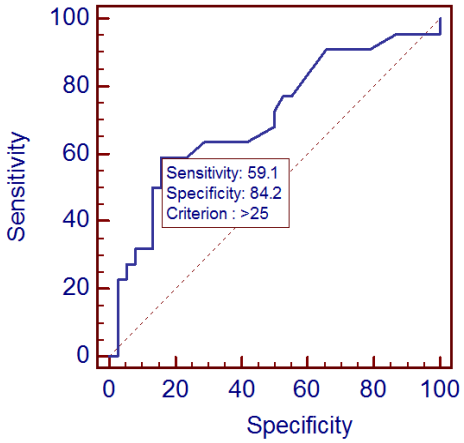

Figure 4. ROC curve for microalbuminuria and Left ventricular hypertrophy

Area under the ROC curve (AUC)	0.835
Standard Error[a]	0.0577
95% Confidence interval[b]	0.716 to 0.918
z statistic	5.797
Significance level P (Area=0.5)	<0.0001

[a] DeLong et al., 1988, [b] Binomial exact

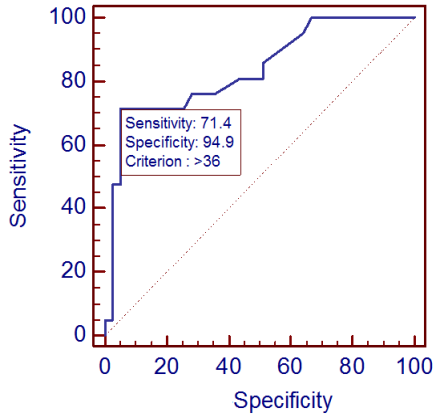

Figure 5. ROC curve for Microalbuminuria and Hypertensive Retinopathy

Area under the ROC curve (AUC)	0.705
Standard Error[a]	0.0734
95% Confidence interval[b]	0.573 to 0.816
z statistic	2.796
Significance level P (Area=0.5)	0.0052

[a] DeLong et al., 1988
[b] Binomial exact

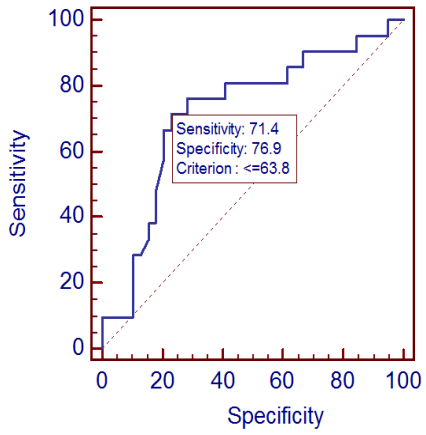

Figure 6. ROC curve for creatinine clearance and Left ventricular hypertrophy

Area under the ROC curve (AUC)	0.721
Standard Error[a]	0.0725
95% Confidence interval[b]	0.590 to 0.829
z statistic	3.049
Significance level P (Area=0.5)	0.0023

[a] DeLong et al., 1988 [b] Binomial exact

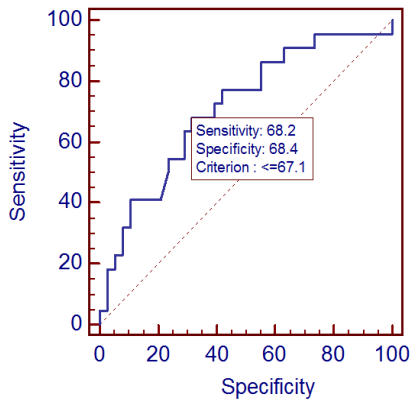

Figure 7. ROC curve for creatinine clearance and hypertensive retinopathy

Area under the ROC curve (AUC)	0.711
Standard Error[a]	0.0707
95% Confidence interval[b]	0.579 to 0.820
z statistic	2.978
Significance level P (Area=0.5)	0.0029

[a] DeLong et al., 1988,
[b] Binomial exact

DISCUSSION

The results of the study show heavy burden of the disease in these asymptomatic subjects as 53% of subjects were found to have TOD. To our knowledge this was the first study to evaluate the relationship of both urine microalbumin and creatinine clearance with TOD in asymptomatic hypertensive Indian population. This study showed that relatively mild degrees of renal dysfunction i.e. presence of urine microalbumin or reduced creatinine clearance was associated with increased cardiovascular damage in the form of LVH or retinopathy. LVH was the most prevalent TOD followed by hypertensive retinopathy. In addition, TOD was more prevalent in hypertensive males than in females. Studies involving different population have shown similar high rates of TOD.[8,9,10,11]

Hypertensive subjects found to have a UA > 30 mg/d in this study was at 30 times more risk developing subclinical target organ damage [95% CI: 3.6-253,p 0.001]. Similarly if the creatinine clearance was less than 60 ml/min/1.73m^2, there was 5.9 times more risk of developing subclinical target organ damage [95% CI: 1.7-19.4, p 0.0035]. But in those patients who were positive for both combined urine microalbumin and reduced creatinine clearance the risk was much higher than either one of them alone i.e. 39.4 times more risk of developing subclinical target organ damage [95% CI: 2.2-703, p 0.0124]. This finding shows that a combined effect of microalbuminuria and reduced creatinine clearance is synergistic in increasing risk for target organ damage and hence would invariably have an effect on prognosis also. There is increasing evidence that a combination of two when present have a grave prognosis than either of them alone. This is shown in studies by Leoncini G [12] et al (2004), Viazzi F [13] et al (2010) , Salles GF [14] et al (2011).

The results of the present study are in concurrence with various previous studies observing that presence of mild renal dysfunction was associated with subclinical TOD and an increased cardiovascular mortality.

It has been well established that patients in end-stage renal disease had a high cardiovascular mortality. But recently, a mild reduced creatinine clearance as a risk factor for cardiovascular mortality and morbidity has been gaining traction. Although various studies showed that a high normal creatinine was an independent and equally important marker of cardiovascular events, it was Fried LP et al [15] who showed that a decrease of GFR < 70 ml/min resulted in a progressive increase of 3 year mortality from cardiovascular events. Later in the HOT study [16] a reduced creatinine clearance <60 ml/min was associated with 3.2 times greater incidence of fatal events. The subsequent HOORN study [17] observed a fourfold risk of cardiovascular death when GFR decreased from 90 to 60ml/min. Recent studies by Leonicini G [12] and Das SK [18] has shown similar association between reduced creatinine clearance and TOD in subclinical hypertensive patients with normal creatinine.

Overt albuminuria has been long associated with cardiovascular mortality and morbidity both in diabetic and non diabetic populations. After the concept of microalbuminuria by Keen in 1960, studies have proved it as a reliable maker of generalized vascular endothelial dysfunction establishing its role as an indicator of early target organ damage in hypertensive patients. The PREVENT study [19] showed that microalbuminuria in hypertensive subjects was independently associated with myocardial ischemia and infarction. The MAGIC study [20] showed that those hypertensive patients with microalbuminuria had LVH and an increase risk of hypertensive retinopathy, acute coronary syndrome, arthrosclerosis and stroke. Recently a meta-analysis of 1 million subjects has shown that an increasing microalbuminuria was associated with increase in deaths from all cause in a continuous manner with no threshold effect.

Left ventricular hypertrophy seen in hypertensive patients as a result of mechanical stress and neurohormonal mechanisms is a reliable marker of TOD. LVH was present in 21 subjects (35%).In subjects with CCR < 60 ml/min vs CCR > 60 ml/min the percentage of LVH was 60% vs 18%(p 0.002). Similar results were shown by Das SK [18] (55% VS 20%, p.001) and Giovanna Leoncini [12] et al (71% VS 42%, p= 0.0001). In subjects with UA > 30 mg/d vs UA< 30 mg/d the percentage of LVH was 83% vs 14%.(p<0.001). Similar results seen with Das SK (78.57% vs 15.38%, p= .000) but lower percentages were seen with Kirsten [21] (30% vs 9%, p<0.001). The significance of

this is that in patients with left ventricular hypertrophy (especially the concentric type) there was a higher risk of developing a coronary event or a destroke as compared to those with normal left ventricular geometry.[22]

Hypertensive retinopathy was present in 22 subjects (36%). This was similar to the hypertensive retinopathies observed by Ghanshyam et al [23] at 38%. In our study we observed UA > 30 mg/d increased the risk of of retinopathy by 6.4 times. In subjects with UA > 30 mg/d vs UA<30 mg/d the percentage of retinopathy were 66% vs 23% (p 0.001). Ghanshyam et al got slightly higher percentage (78.1% vs 14.5, p <0.001). Retinopathy was found in 52% of subjects with CCR < 60ml/min while it was present in only 27% subjects with normal CCR (p < 0.049).

In this study, we found negative significant correlation between microalbuminuria and CCR clearance (r -0.498 , p < 0.001). This finding is consistent with results observed by Das

SK[18] (r -0.314, p 0.004) and De La Sierra et al [24] who showed a serum creatinine >88 pmol/L (odds ratio:3.08; CI 95%: 1.39-6.84) was independently associated with increased urinary albumin excretion.

The importance of our study is that as the prevalence of hypertension, a life style modifiable disease in India is expected to rise with increasing urbanisation, so is the burden of the comorbidities even in asymptomatic hypertensive patients (53% in the present study). In our study there has been a strong association between reduced creatinine clearance, microalbumin and the presence of LVH or retinopathy. The development of subclinical cardiovascular damage, such as hypertensive retinopathy and/or LVH,[25] often precedes and predicts the acute onset of major events and has proven to be a powerful independent predictor of cardiovascular prognosis.[26]

The association of various risk factors in this study with both MA and CCR in part explains the finding of TOD even thought they were asymptomatic. These traditional risk factors in association with uncontrolled hypertension caused unfavourable functional and structural organ changes along with the acceleration of development of atherosclerosis resulting in TOD in these subjects. Both MA and CCR<60ml/min were associated with an unfavourable lipid profile (p< 0.001 & p<0.001) and increasing duration of the disease (p<0.004 & p<0.001). But microalbuminuria had additional significant association with BMI (p<0.05) and severity of SBP/DBP (p<0.002). As a result of these associated risk factors being more for MA, our study showed that MA predicted TOD more significantly than a CCR< 60 ml/min at 30 times (p<0.001) vs 5.9 times (p<0.003).

CONCLUSION

Although preventing target organ damage is more important than treating it, with the help of these renal markers early detection of organ damage in these asymptomatic hypertensive subjects can be aimed for. This will in turn result in a tighter control of BP so as to aid in regression of the organ damage and improve the overall prognosis. A wider application of these tests could significantly improve the cost-effectiveness of the diagnostic approach in patients with hypertension. This may lead to a substantial improvement in identifying high risk patients while optimizing the cost effectiveness of CV risk stratification.

CONFLICT OF INTEREST

Nil.

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