A comparative study to determine the better predictor of renal impairment in essential hypertensive patients

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Abstract

Introduction and Objectives: Hypertension (HTN) is one of the major public health problems of adult population. HTN and renal functions are closely related and it is a predisposing factor for renal abnormalities. The objectives of the study were to estimate and compare the levels of Microalbuminuria (MAU), serum creatinine and estimated Glomerular Filtration Rate (eGFR) in essential hypertensives and to correlate their levels with duration of HTN.

Materials and Methods: The data of the cross sectional study includes physical measurements, blood pressure and biochemical investigations like serum creatinine, MAU [measured using Albumin Creatinine Ratio (ACR)] & eGFR.

Result: Out of 220 subjects, 112 (48.21% male and 51.78% female) were essential hypertensives and 112 (47.32% male and 52.68% female) were non-hypertensives. Mean value of serum creatinine was within the normal range in both the study groups. 62.5% hypertensives had MAU as compared to 4.46% non-hypertensives. The difference in eGFR was not statistically significant among the study groups. Receiver Operative Characteristic curve (ROC) for duration of HTN showed that area under the curve for MAU was more as compared to serum creatinine and eGFR.

Conclusion: HTN is a non-communicable disease (NCD) that still remains inadequately treated. The kidney is considered as a prime target for hypertensive damage. Our study suggests that MAU is prevalent in essential hypertensive subjects and has a positive correlation with the duration of HTN. MAU can be used as a better predictor of renal impairment in essential hypertensive patients as compared to serum creatinine and eGFR. More extensive screening for MAU should be performed to facilitate better stratification of renal disease in hypertensive patients.

Keywords: HTN, Serum creatinine, MAU, ACR & eGFR.

Introduction

Hypertension (HTN) is one of the biggest health challenges in the 21st century causing about 9.4 million deaths every year and it is the leading cause of premature death. The incidence of HTN in India is 5-15%.[1] According to World Health Organization (WHO) health statistics 2012, the prevalence of HTN in India was 23.1% in men and 22.6% in women of the age of 25 years or more.[2]

HTN results from complex interactions of genes and environmental factors and hence it is difficult to understand the exact cause of it.[3] HTN doubles the risk of Cardio-Vascular Disease (CVD) and it also increases the risk of developing cerebrovascular accidents and renal diseases.[4]

Chronic uncontrolled HTN leads to renal diseases and it is symptomless in the early stage. Patients don't realize that they have a problem until their renal function has decreased to less than 25% of the normal renal functional capacity. Hence, a better biomarker that allows detection of renal damage in the early stages is essential for the diagnosis.[5]

"Sir Robert Hutchinson's words from the beginning of 20th century are still appropriate today at the beginning of 21st century: "The ghosts of dead patients that haunt us do not ask why we did not employ the latest fad of clinical investigation. They ask us, why did you not test my urine?"

Screening for MAU is a sensitive, reliable and accessible test and it is an independent risk factor for renal disease and cardiovascular morbidity and mortality.[6] Screening for MAU can be performed by three methods:[7]

1. Measurement of the Albumin-Creatinine Ratio (ACR) in a random spot collection of urine
2. Measurement of MAU in 24-hour collection of urine and
3. Measurement of MAU in timed (e.g., 4-hours or overnight) urine sample.

The American Diabetic Association (ADA) guidelines of 2004 recommend the use of Urinary Albumin Excretion (UAE) or ACR on random samples. According to ADA, 24 hours urine collection is the gold standard method for measuring UAE. However, more convenient method to detect MAU in clinical practice is the ACR in a random urine sample and ACR correlates very well with MAU measured in 24-hour urine samples.[8,9]

Therefore in our study we have used ACR on spot urine samples to measure microalbuminuria. (Table 1)

Estimation of serum creatinine is a simple and the most commonly used biomarker of renal function. But, it may remain within the normal range even with a decrease in glomerular filtration rate (GFR) of $> 50\%$.[11]

The first step in the prevention of renal insufficiency is early diagnosis and treatment. One of the best markers to assess the renal function is the GFR.[12] Accurate estimation of GFR requires the use of invasive techniques which is difficult to perform routinely in daily practice.[13,14]

To overcome this, endogenous biomarkers like serum creatinine and cystatin-C have been used as markers for estimation of GFR to assess the renal functional status.[15]

Various formulae have been derived based on serum creatinine. One such commonly used equation is the Modification of Diet in Renal Disease (MDRD) equation.[16]

The association between essential HTN and renal disease has received little consideration because of its asymptomatic nature. Hence, the present study was undertaken to determine the correlation between the HTN, serum creatinine, MAU and eGFR and also to determine the better predictor of renal function impairment in essential hypertensive patients.

Materials and Methods

This was a cross sectional study carried out in essential hypertensive patients visiting the outpatient clinic of department of General Medicine, Mandya Institute of Medical Sciences and teaching Hospital (MIMS), Mandya. Consented individuals were included in the study, after obtaining relevant clearance from the Institutional Scientific Committee and the Institutional Ethics Committee of MIMS, Mandya.

By purposive sampling method, 224 subjects in the age group of 30–60 years who were enrolled were included in the study. According to JNC-VII and inclusion and exclusion criteriae, 112 subjects were included in hypertensive group and an equal number of age- sex matched subjects were included in non-hypertensive groups.[17]

Those who were known cases of secondary HTN, diabetes mellitus, patients with known thyroid disorders, urinary Tract Infections, pregnant and lactating women, haematuria and acute illness were excluded from the study.

Collection of Data: A participant proforma was used to record information regarding demographic history, family history and anthropometric measurements like weight, height, Body Mass Index (BMI), blood pressure and biochemical investigations. About 3ml of venous blood sample was drawn under aseptic precautions. Participants were instructed to collect random mid-stream urine sample in a sterile container for the study. In women, urine was collected during the non-menstrual phase of their cycles. 1:10 diluted urine sample was used for the estimation of urine creatinine. Serum creatinine and urine creatinine were estimated by Modified Jaffe's method. Albumin level in the urine sample was estimated by Immuno-turbodometry method using MISPA-I. MAU was expressed using ACR. eGFR was calculated using serum creatinine by MDRD formula.

Statistical Analysis

Data was entered into Microsoft Excel sheet and analyzed using SPSSv15 software. Means of various groups were compared using students t-test. Inferential statistical tests like chi-square test and ROC were used to analyze categorical data. The statistical significance was evaluated at 95% confidence level and p value less than 0.05 was considered as statistically significant.

Results

(Table 2) Out of 112 hypertensives, 54 subjects were males and 58 were females and among non-hypertensive subjects 53 were males and 59 were females. There is no statistical difference among the different class of age groups.

(Graph 1) According to WHO classification of BMI[18] more than half of the hypertensive subjects (50.9%) were verweight/obese as compared to non-hypertensives (35.7%).

Biochemical parameters between hypertensives and non-hypertensives: (Table 3) Majority of the individuals had normal serum creatinine in both hypertensives and non-hypertensives and there was no statistical significant difference between the two groups.

(Graph 2) It was found that majority of the individuals in the hypertensives group had MAU as compared to non-hypertensives. There was a statistical difference of MAU among hypertensives as compared to non-hypertensives.

(Table 4) It was found that, 50.89% (57) hypertensives were found to be having decreased eGFR ($< 90ml/min/1.73m^2$) as compared to 39.29% (44) non-hypertensives. Even though the percentage of hypertensives having decreased eGFR was higher as compared to non-hypertensives, it was not statistically significant.

(Table 5) In the present study it was found that, the mean values of SBP and DBP were significantly high among hypertensives as compared to non-hypertensives. In case of serum creatinine, the mean value was higher in hypertensives than non-hypertensives but it did not show significant difference between the two groups. Whereas in case of MAU, hypertensives individuals had a significantly higher mean value as compared to non-hypertensives and it was found to be statistically significant. Even though the mean value of $eGFR_{MDRD}$ in hypertensives was lower as compared to non – hypertensives, it did not show significant difference.

Comparisons of biochemical parameters with duration of hypertension: (Graph 3) In the present study it was found that, among 42 hypertensives with duration of more than 5 years, 90.48% (38) had MAU and 9.52% (4) subjects did not have MAU and it was statistically significant.

(Graph 4) From the above ROC curve it was found that, the area under the curve for MAU was 0.714, eGFR – 0.575 and for serum creatinine - 0.491 with duration of HTN. Area under the curve for MAU was more as compared to other two parameters and hence in our study population, MAU emerged as biomarker to assess the renal impairment with duration of HTN.

Discussion

Hypertension is a major public health problem and it is a complex multifactorial disorder. High BP is an important independent predictor of the development and progression of renal disease.[19]

MAU and vascular disease are known to occur early in the course of Essential HTN. MAU is a reversible component that expresses the cellular and molecular status of the renal function. The prevalence of renal disease is

severely underestimated when it is defined on the basis of serum creatinine level instead of GFR.[20]

The prevalence of hypertension is high in India and hypertensive nephropathy is a common cause of chronic kidney disease. Hence the present study was undertaken to evaluate the association of serum creatinine, MAU (estimated using ACR) and eGFR among hypertensive and non-hypertensive individuals to determine the better predictor of renal impairment.

In concurrence with our study (Graph 1), the third National Health and Nutrition Examination Survey (NHANES III) showed an increasing rate of hypertension with increasing BMI.[21]

In contrast to our study (Table 2), a study done by Wannamethee et al, showed that serum creatinine was elevated in 13.8% of hypertensives cases and in 8.6% of normotensive subjects and it was statistically significant.[22]

In 1991, Stefano Bianchi et al published the first large study on the prevalence of MAU among hypertensives and it was found to be 35%. Another study by Tsioufis et al in 2002 reported a prevalence of 47% among hypertensives.[23]

The variability in prevalence may be explained by different cut-off values used to define MAU, method of urine collection, different protocols used to evaluate MAU and the characteristics of study population.[23]

As seen in the (Graph 2), the high percentage MAU in patients with essential HTN must alert the clinician regarding impairment of renal function. Roberto P et al, showed that ACR values were higher in cases as compared to controls.[24]

In concurrence with our study (Table 4), the study done by Malarkodi V; showed that, 44.5% non-hypertensives with normal serum creatinine levels had reduced eGFR values as estimated by MDRD equation.[25]

Table 1: Diagnostic criteria for Microalbumin excretion[9,10]

Category	Spot collection of urine sample in ACR (mg/gm creatinine)	24-h collection urine sample (mg/24h)	Timed collection of urine (µg/min)
Normal	< 30	< 30	< 20
MAU	30-299	30-299	20-199
Macroalbuminuria	≥ 300	≥ 300	≥200

Table 2: Distribution of study subjects according to age and gender

Age groups (Years)	Hypertensives Number (%)		Non-Hypertensives Number (%)		p value
	Males	**Females**	**Males**	**Females**	
30 – 40	8 (44.44)	10 (55.55)	23 (44.23)	29 (55.77)	p > 0.05
41 – 50	15 (48.38)	16 (51.61)	12 (46.15)	14 (53.85)	
51 – 60	31 (49.20)	32 (50.79)	18 (52.94)	16 (47.06)	
Total	54 (48.21)	58 (51.78)	53 (47.32)	59 (52.68)	

Graph 1: Distribution of BMI among hypertensives and non-hypertensives
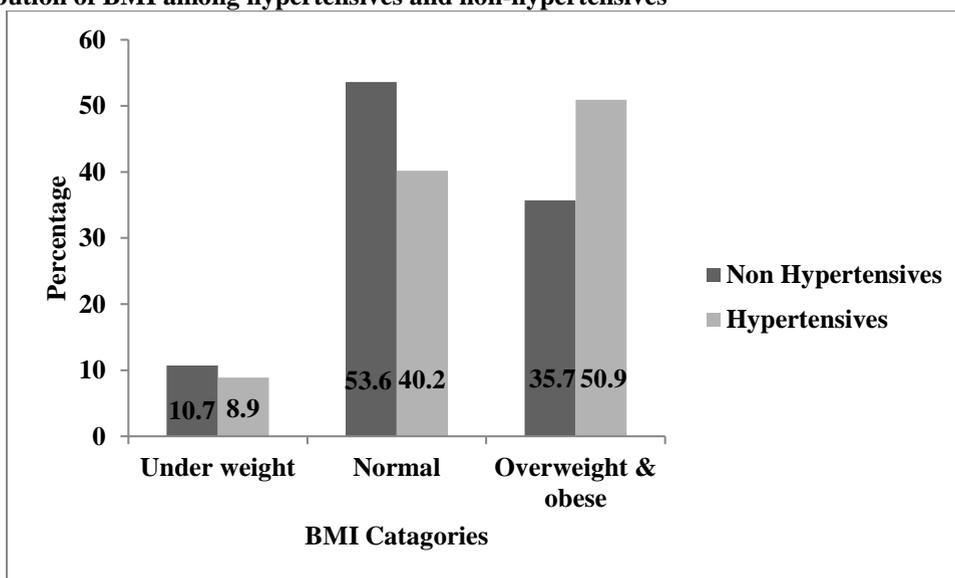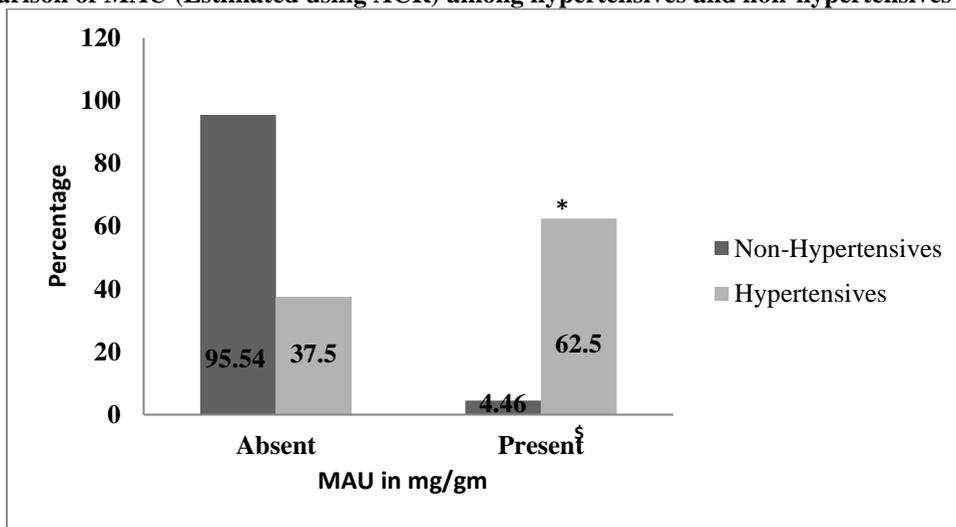
Table 3: Comparison of serum creatinine between hypertensives and non-hypertensives[14]

Serum creatinine mg/dl	Hypertensives		Non-Hypertensives		p value
	Number	%	Number	%	
Normal	111	99.1	111	99.1	
Abnormal	1	0.9	1	0.9	>0.05
Total	112	100	112	100	

Graph 2: Comparison of MAU (Estimated using ACR) among hypertensives and non-hypertensives

$^{\$}$MAU > 30mg/gm of ACR and * statistically significant.

**Table 4: Comparison of eGFR$_{MDRD}$ among hypertensives and non-hypertensives**

eGFR ml/min/1.73m^2	Hypertensives		Non-hypertensives		p value
	Number	%	Number	%	
≥ 90	55	49.11	68	60.71	
< 90	57	50.89	44	39.29	> 0.05
Total	112	100	112	100	

Table 5: Comparison of mean values of SBP, DBP, serum creatinine, MAU$^{\#}$ and eGFR$_{MDRD}$ between hypertensives and non-hypertensives

| Parameters	Hypertensives Mean ± SD	Non-hypertensives Mean ± SD	p value
SBP (mm Hg)	146.29 ±17.45	110.39 ± 11.29	< 0.01*
DBP (mm Hg)	91.52 ± 12.27	71.20 ± 7.37	< 0.01*
Serum creatinine (mg/dl)	0.84 ± 0.16	0.78 ± 0 .13	> 0.05
MAU$^{\#}$ (mg/gm)	70.65 ± 65.94	13.28 ± 8.28	< 0.01*
eGFR$_{MDRD}$ (ml/min/1.73m^2)	92.97 ±18.52	95.99 ± 17.81	> 0.05

$^{\#}$ estimated using ACR and * statistically significant.

Graph 3: Distribution of MAU (estimated using ACR) with duration of HTN
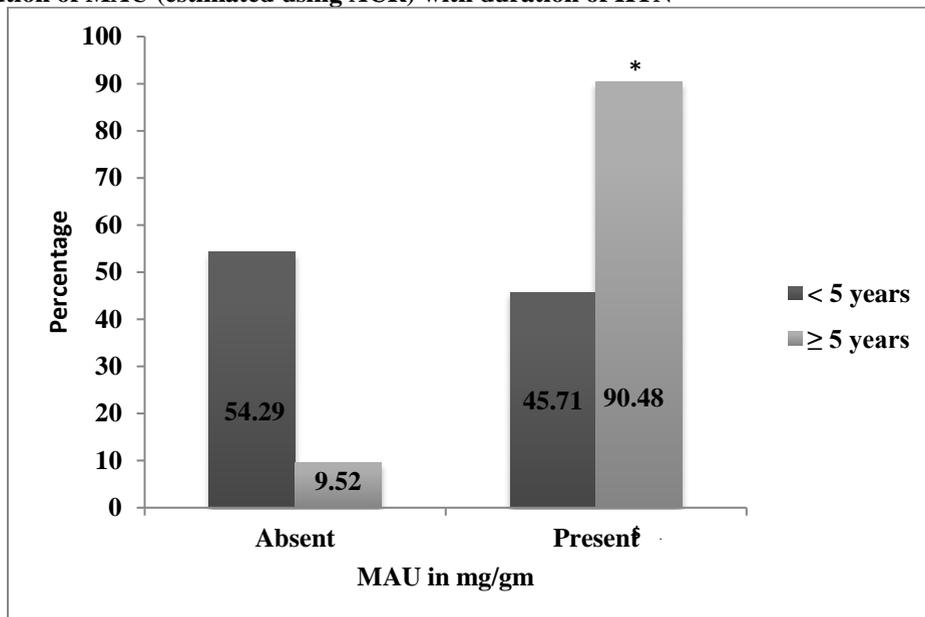
$^\$$ MAU > 30mg/gm of ACR & * statistically significant.

Graph 4 - Receiver Operating Characteristic (ROC) curve to compare serum creatinine, MAU$^\#$ & eGFR$_{MDRD}$ with duration of HTN
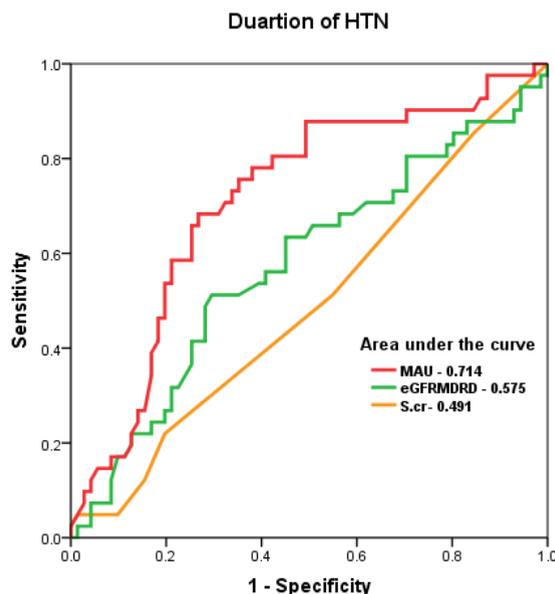
$^\#$ calculated using ACR

Limitations of the Study

A 24 hour urine sample is the gold standard to measure MAU, but, it could not be collected in the present study.

There are many limitations in the calculation of eGFR$_{MDRD}$ using serum creatinine, to assess renal impairment. Hence requires gold standard method for the early detection of renal impairments in hypertensive patients.

Scope for Further Studies

There is lot of confusion about reporting of results in different units. Ideally, International System of Units should be adopted to express the results for each of the parameters.

There is a need to further evaluate and re-establish the normal reference ranges of eGFR, according to each of the formulae and for different ethnic groups.

Conflict of Interest: None.

Conclusion

HTN is a major health problem in the community; a significant proportion of which still remains inadequately treated. Kidney is considered as prime target of hypertensive damage. Serum creatinine alone can be difficult to assess renal functional status at the earliest. The prevalence of MAU varies in different population groups, based on the characteristics of the population as well as techniques and protocols used for its evaluation.

The prevalence of MAU increases with the duration of HTN. Early screening of essential hypertensive patients for MAU and aggressive management of HTN might reduce the burden of diseases due to renal damage secondary to HTN in the community. The advantage of using eGFR as calculated by MDRD formula is based on its simplicity, ease of reporting and cost effectiveness. However, the MDRD equation is not without its limitations. Some studies have shown that MDRD equations may underestimate GFR in healthier populations. Thus, it may lead to misdiagnosis and misclassification of CKD in individuals with mild renal insufficiency.[25]

More extensive screening for MAU should be performed among hypertensive subjects to facilitate better stratification of renal disease in patients with essential HTN.

Our study suggests that MAU is prevalent in essential hypertensive patients and has a positive correlation with the duration of HTN and thus can be used as an early marker for end stage renal damage.

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