Microalbuminuria and Red Cell Distribution Width as Predictive Markers of Renal Involvement in Hypertension

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Background: The adverse outcomes of chronic kidney disease (CKD) in particular, progression to overt renal failure and development of cardiovascular disease (CVD), can be prevented or delayed by early detection and appropriate treatment. Effective diagnosis and management of hypertension is a crucial component of such efforts.

Objective: The present study was undertaken to assess the changes, if any, in red cell distribution width (RDW) and microalbuminuria in patients at different stages of Hypertension (HT) and to evaluate the usefulness of these markers in predicting the renal involvement.

Materials and Methods: This study was conducted in 117 patients with clinically proved hypertension under treatment and 63 age and sex matched healthy adults, to evaluate the usefulness of red cell distribution width (RDW) and urine microalbumin, as predictive markers of renal involvement.

Results: A significant elevation in excretion of microalbumin was observed in patients at different stages of hypertension compared to the normal controls. RDW of the test group was significantly higher than that of the control group. When RDW was compared stage wise the value was significantly higher only in stage 2 compared to normal and stage 1 hypertensive patients.

Conclusion: The elevation of urine microalbumin and its association with elevated RDW, which is an emerging cardiovascular risk predictor, suggests endothelial dysfunction in chronic hypertensive patients. Hence periodic monitoring of these markers may be of use in predicting the renal involvement in hypertension.

Keywords: Hypertension, Chronic Kidney Disease, End Stage Renal Disease, Red Cell Distribution Width, Microalbuminuria

INTRODUCTION

Hypertension (HT) is an important public health challenge in both economically developing and developed countries, the prevalence of which varies worldwide[1]. Overall 20% of the world's adults are estimated to have hypertension. Epidemiological studies show a steadily increasing trend in the prevalence of HT over the last 40 years, more in urban than in rural areas. There is a strong correlation between changing lifestyle factors and increase in HT in India[2]. Approximately 1 billion people have hypertension and contributing to more than 7.1 million deaths per year throughout the world. There is growing evidence that some of the adverse outcomes of chronic kidney disease (CKD) in particular, progression to overt renal failure and development of cardiovascular disease (CVD), can be prevented or delayed by early detection and appropriate treatment. Effective diagnosis and management of hypertension is a crucial component of such efforts.

High blood pressure is one of the leading causes of kidney failure and in advanced stages; renal failure will occur. Renal hypertension puts stress and increased pressure on the kidney, and is a major cause of end-stage renal disease, also known as chronic renal disease, in the elderly. CKD defined by the National Kidney Foundation as the presence of kidney damage or decreased level of kidney function for at least 3 months, is a worldwide public health problem with a rising incidence and prevalence. Currently, over 26 million American adults have CKD[3]. Hypertensive nephropathy is a medical condition referring to damage to the kidney due to chronic high blood pressure. It should be distinguished from renovascular hypertension, which is a form of secondary hypertension. Additional complications often associated with hypertensive nephropathy include glomerular damage resulting in proteinuria and haematuria[4]. Hypertension is both a common cause and complication of CKD.

Early kidney disease is a silent problem, like high blood pressure, and does not have any symptoms. People may have CKD but are not aware of it because they do not feel sick. It is an insidious disease, and patients with hypertension and diabetes, need to be assessed regularly and managed in line with established guidelines[5]. The appropriate evaluation and treatment of hypertension is critical in caring for patients with CKD, as uncontrolled blood pressure can lead to faster decline in kidney function and accelerated development of cardiovascular disease, which is the leading cause of death for CKD patients. As the prevalence of these risk factors associated to CKD is at an alarming rate, no country can afford to overlook the burden of CKD; therefore prevention, early detection, and intervention are the only cost-effective strategies. Prevention of end stage renal disease (ESRD) by early detection and treatment is an important tool to stop the growing need for renal replacement therapy. Evaluation of hypertensive patients for the presence of CKD is critical as part of preventive care and treatment strategies. Measurement of urinary albumin excretion can serve as a screening test for CKD in hypertensive patients. The normal rate of urinary albumin excretion is less than 20 mg/day. Persistent albumin excretion between 30 and 300 mg/day is termed microalbuminuria, while albumin excretion above 300 mg/day is considered macroalbuminuria[6].

Albuminuria is considered a key aspect of the pathogenesis of progressive kidney dysfunction, which independently predicts cardiovascular and renal outcomes in hypertension. It has been suggested that microalbuminuria may represent the renal manifestation of vascular endothelial dysfunction[7], which is frequently seen in patients with established essential hypertension, and is a predictor of a higher risk for cardiovascular and probably renal dysfunction. Microalbuminuria seems to constitute a simple and accurate method to detect a hypertensive patient at a high risk for cardiovascular and probably renal damage. National Kidney Foundation and American Heart Association recommend combined screening for microalbuminuria and estimated GFR with the Modification of Diet in Renal Disease (MDRD) study equation for all adult patients with CVD as well as those with risk factors for CKD, such as diabetes, hypertension, family history of kidney disease, and obesity[6].

Table 1: Classification of Blood Pressure for Adults according to JNC 7		
Blood Pressure Classification	**Systolic BP (mm Hg)**	**Diasystolic BP (mm Hg)**
Normal	< 120	and < 80
Prehypertension	120 - 139	or 80 - 89
Stage 1 hypertension	140 - 159	or 90 - 99
Stage 2 hypertension	≥ 160	or ≥ 100

Clustering microalbuminuria with other markers of endothelial function such as red cell distribution width (RDW) may contributes to the prediction of renal outcomes in hypertension. The RDW is a measure of the variation of red blood cell width that is reported as part of a standard complete blood count. Usually red blood cells are a standard size of about 6–8µm.

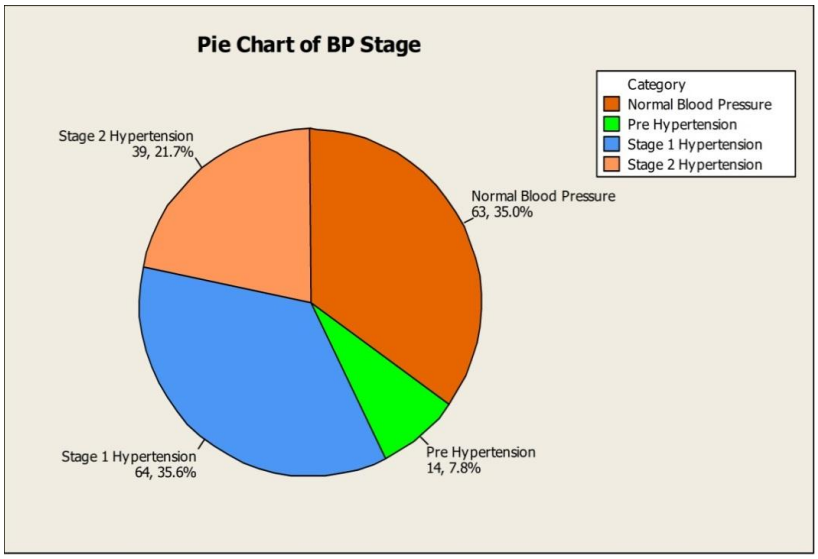

Figure 1 : Classification of patients according to Blood Pressure

Certain disorders, however, cause a significant variation in cell size. Higher RDW values indicate greater variation in size. Normal reference range in human red blood cells is 11%–15%. An elevated RDW is known as anisocytosis. RDW has been very recently reported to be a strong and independent predictor of adverse outcomes in the general population[8]. High RDW may be associated with adverse outcomes in patients with HT[9] and recently it was shown that RDW was significantly related to major cardiovascular events in patient with heart failure even after adjustment of haematocrit values[10].

The present study was undertaken to assess the changes, if any, in RDW and microalbuminuria in patients at different stages of HT and to evaluate the usefulness of these markers in predicting the renal involvement in HT.

MATERIALS AND METHODS

The study was conducted at Hrithayalaya Institute for Preventive Cardiology Trivandrum, Kerala for a period of 1 year from January to December 2011 after getting approval from our Institutional Ethics Committee. One hundred and seventeen hypertensive patients below the age of 65 years formed the test group. The control group consisted of 63 subjects selected from the siblings and staff of the institutes. Detailed clinical, epidemiological and anthropometric characteristics were recorded using proforma. The auscultatory method of BP measurement with a properly calibrated and validated instrument was used (Elko mercurial sphygmomanometer). At least 2 measurements were made. The test group was classified based on blood pressure into 4 classes(**Fig.1**) based on the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) [11] as given in the **Table 1.**

5 ml. of venous blood and 24 hour urine samples were collected from all the subjects after getting the informed consent, as per the criteria laid down by the Institutional Ethics Committee. Blood collected in EDTA was mixed by inversion several times and used for complete blood cell count (CBC) using BC 5800

Table 2 : Descriptive statistics of test and control groups

	BP Stage	n	Mean	Std. Deviation	t value	p value
Height	Test	117	165.21	7.38	1.057	NS
	Control	63	166.52	7.65		
Weight	Test	117	70.74	9.68	-2.711	.007*
	Control	63	66.98	8.19		
BP Systolic	Test	117	155.21	23.05	-13.31	.000*
	Control	63	111.41	7.65		
BP Diastolic	Test	117	93.50	12.65	-10.29	.000*
	Control	63	73.90	5.15		
RDW	Test	117	13.62	2.43	-2.315	.022*
	Control	63	13.05	1.41		
Microalbuminuria	Test	117	53.89	51.08	-5.750	.000*
	Control	63	16.59	8.78		

NS – Not Significant, * - Significant – p< 0.05

Table 3: Group Statistics RDW

	BP Stage	n	Mean	Std. Deviation	Std. Error Mean
RDW	Normal	63	13.05	1.41	0.18
	Pre HT	14	12.36	2.21	0.59
	Stage 1 HT	64	13.72	2.47	0.31
	Stage 2 HT	39	13.90	2.37	0.38

Auto Haematology Analyser of Mindray. Microalbumin was estimated using particle-enhanced turbidimetric inhibition immunoassay adapted to the Dimension clinical chemistry system which allows direct quantitation of microalbumin in urine samples.

Statistical analysis

All results were expressed as mean ± SD. Independent sample't' test was performed. Statistics were done using SPSS ver 17 and Minitab ver 15 for comparing the markers at different stages of hypertension. ANOVA of RDW was carried out against different stages of HT. Correlations of parameters were analysed using Karl Pearson correlation coefficient[12]. Probability values of $p<0.05$ were considered to be significant.

RESULTS

There were 180 subjects in the present study with mean age 50 ±15. The descriptive statistics of the sample is given in **Table 2**. The male to female ratio of the sample was 57: 43. The test group was classified based on JNC 7 and the results are given in **Figure 1**. For the present study only two parameters namely, RDW, and

Urine microalbumin were taken for analysis. One way ANOVA of RDW was carried out against different stages of HT and is given in **Table 3** and **Table 4**. One way ANOVA of RDW against different stages of HT shows significant differences **(Table 4)**. Kruskal-Wallis test of microalbuminuria against different stages of HT was also carried out and is given in **Table 5**. Similarly Kruskal – Wallis test of microalbuminuria against different stages of HT also shows significant difference **(Table 5)**. Group statistics and p values of RDW at different stages of blood pressure are given in **Figure 2** and **Table 6.** Group statistics of Microalbuminuria is given in **Table 7** and **Figure 3**. We could not find any correlation between microalbuminuria and RDW **(Table 8)**.

Table 4: One way ANOVA of RDW against different stages of HT

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	39.151	3	13.050	2.935	.035
Within Groups	782.599	176	4.447		
Total	821.750	179			

Table 5 : Kruskal-Wallis statistic of Microalbuminuria of different BP stages

	BP Stage	n	Median	Inter Quartile Range	p Value
MICROALBUMINURIA	Normal	63	16.00	12.00	0.000
	Pre HT	14	48.50	53.80	
	Stage 1 HT	64	32.00	29.00	
	Stage 2 HT	39	37.00	31.00	
	Total	180			

Table 6: t test p values of RDW at different BP Stages

	Normal	Pre HT	Stage 1 HT	Stage 2 HT
Normal	*	0.142	0.062	0.025
Pre HT	0.142	*	0.061	0.039
Stage 1 HT	0.062	0.061	*	0.718
Stage 2 HT	0.025	0.039	0.718	*

DISCUSSION

Hypertension is one of the most important public health problems resulting in high morbidity and mortality this is due to the risk of CV and CKD. Because of HT the heart works harder and can damage the blood vessels

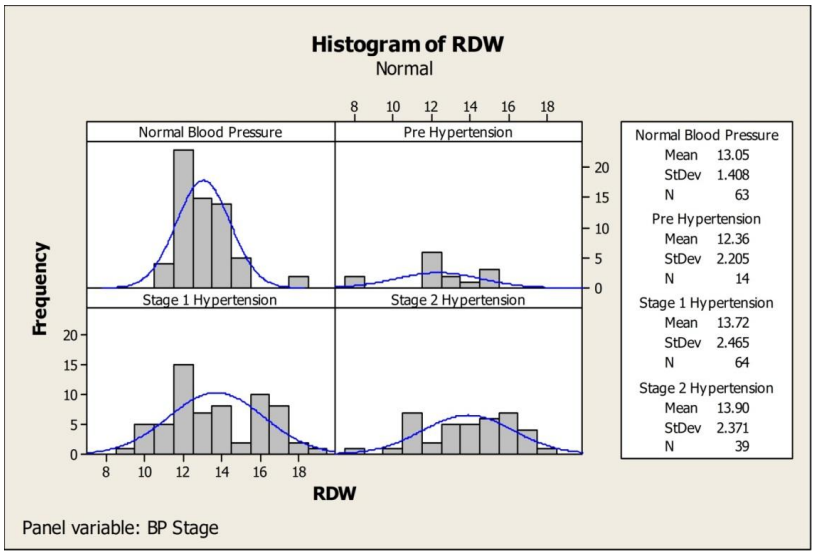

Figure 2: Group Statistics of RDW at different stages of Blood Pressure

throughout the body resulting in endothelial dysfunction and vascular damage. The damage of the blood vessels in the kidneys will interfere in filtration and will result in early kidney disease. Impaired kidney may fail to separate blood albumin from the wastes. Damage to the blood vessels will interfere with the filtration process of the kidney and may lead to microalbuminuria which can result in CKD[13].

Estimated GFR (eGFR) based on serum creatinine and/or Cystatin C is reported to be useful for the detection of patients who are at high risk for developing CKD[14]. But eGFR has its limitations in predicting CKD especially when the serum creatinine and/or serum Cystatin C levels are low. Hence studies are conducted all over the world to find out a better, reliable and cost effective marker for the early detection of renal involvement. RDW is automatically recorded in any automated haematology analysers and studies have shown a strong association of RDW and long term mortality risk in critically ill patients[15]. We have earlier observed that RDW and high sensitivity C - reactive protein can be

Table 7: Mann Whitney test p values of Microalbuminuria at different BP Stages

	Normal	Pre HT	Stage 1 HT	Stage 2 HT
Normal	*	0.000	0.000	0.000
Pre HT	0.000	*	0.161	0.413
Stage 1 HT	0.000	0.161	*	0.252
Stage 2 HT	0.000	0.413	0.252	*

Table 8: Correlation between microalbuminuria and RDW

		RDW	MICROALBUMINURIA
RDW	Pearson Correlation	1	.069
	Sig. (2-tailed)		.356
	n	180	180
MICROALBUMINURIA	Pearson Correlation	.069	1
	Sig. (2-tailed)	.356	
	n	180	180

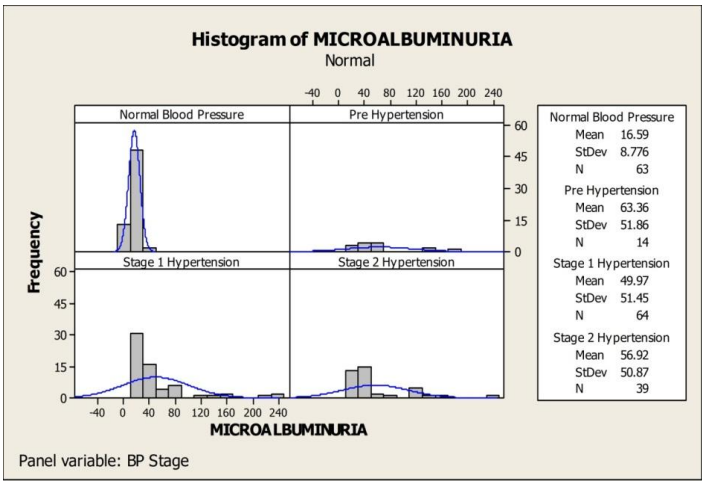

Figure 3: Group statistics of Microalbuminuria

used as risk markers in hypertension[16]. Since the markers had certain limitations in predicting the progression of HT, in the present study an attempt is being made to correlate RDW with microalbuminuria as biomarkers for renal involvement in hypertension.

Data on the predictive role of microalbuminuria in terms of progression of renal damage are scanty in patients with primary hypertension. Screening for microalbuminuria is reported to be an easy and inexpensive test that reveals a potentially treatable abnormality. It is recommended that urinary albumin excretion should be routinely measured in hypertensive patients and in the presence of microalbuminuria; antihypertensive treatment should be intensified in order to obtain an optimal blood pressure control[17]. The present result clearly indicates that microalbuminuria is directly related to the BP and urinary microalbumin excretion increases with the progression of HT. So controlling of BP is useful in reducing microalbuminuria and preventing the renal involvement in HT.

RDW levels were reported to be elevated in nutrient deficiencies such as iron, vitamin B_{12} and folate which may contribute to physiological changes resulting in clinical consequence[18]. Lippi et al reported an inverse association between RDW and kidney function test[19]. Recent study by Alphonso et al had shown a close association of RDW with renal involvement in CVD. However, the mechanism(s) underlying this association remains unclear. An interaction between chronic inflammation, oxidative stress, neurohumoral over activity and endothelial dysfunction may explain this association[20]. Further research is needed to understand the pathophysiology underlying these effects.

We have observed that both RDW and urinary microalbumin are elevated in patients with HT but the elevation in RDW was not significant. Urinary microalbumin was significantly elevated in all patients with HT irrespective of the stage of the disease. Progression in HT leads to elevation in the excretion of microalbumin and hence it could be of use in predicting the renal involvement in HT. Further studies are required to evaluate the effect of medical intervention for HT in the excretion of microalbumin.

CONCLUSION

This study was conducted to evaluate usefulness of RDW and microalbuminuria as biomarkers of risk in patients with HT. From the results we have observed that both RDW and urinary microalbumin are elevated in patients with HT but the elevation in RDW was not significant. Urinary microalbumin was significantly elevated in all patients with HT irrespective of the stage of the disease. Progression in HT leads to elevation in the excretion of microalbumin and hence it could be of use in predicting the renal involvement in HT. Further studies are required to evaluate the effect of medical intervention for HT in the excretion of microalbumin.

CONFLICTS OF INTEREST

None declared

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