Int J Pharm Bio Sci 2014 July ; 5 (3) : (P) 560 - 568

Research Article **Medicinal chemistry**

International Journal of Pharma and Bio Sciences **ISSN 0975-6299**

TO STUDY GLOMERULAR FILTRATION RATE IN ESSENTIAL HYPERTENSION.

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ABSTRACT

Hypertension is one of the major causes of morbidity and mortality in human population. High blood pressure is a well established threat factor for cardiovascular disease partly because it is proatherogenic and also it facilitates injury to the vascular endothelium via increased stress caused by the flowing of blood. The objective of the study was to determine GFR in prehypertensives and essential hypertensives. Serum creatinine was estimated in autoanalyser by alkaline picrate method and eGFR was calculated using MDRD equation. There is significant decrease in S. creatinine level and increase in eGFR value in prehypertensives as compared to controls. But there is a significant decrease in eGFR value in hypertensives as compared to controls and prehypertensives. The study indicates measuring glomerular filtration rate is a better indicator of ongoing pathophysiological mechanisms and progression of the disease above the measurement of arterial pressure and serum creatinine level in both prehypertensives and hypertensives.

KEY WORDS: **Creatinine, eGFR, glomerular filtration rate, hypertension, prehypertension.**

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INTRODUCTION

Hypertension is a chronic condition characterized by increased tension in the arteries. It is an established risk factor for myocardial infarction, stroke and peripheral vascular disease. It is one of the major causes of cardiovascular morbidity and mortality. A sustained arterial diastolic blood pressure greater than 89 mm of Hg or systolic blood pressure greater than 139 mm of Hg are found to be associated with increased risk of atherosclerosis and renal diseases. Elevated glomerular pressures are required to excrete the increased sodium load which can eventually lead to glomerular scarring and endothelial dysfunction (hyperfiltration injury)[1]. Sympathetic nervous system contributes to the pathogenesis of essential hypertension by affecting renal circulation. Glomerular filtration rate is defined as that amount of blood (passing through kidneys) which is filtered per minute by each kidney. Glomerular filtration rate (GFR) is considered as a better index for measuring overall function of the kidney. Progressive decline in GFR is matched by a reciprocal increase in arterial pressure which helps to sustain sodium and fluid homeostasis in the body[2]. Alteration in glomerular filtration rate can be used as an indicator for subsequent kidney damage[3, 4]. Hyperfiltration is considered to characterize an early and reversible stage of kidney damage[5, 6]. But it is not very clear whether hyperfiltration occurs in early stage of hypertension. The study was undertaken to determine glomerular filtration rate when systolic blood pressure was greater than 120 mm Hg and /or diastolic blood pressure was greater than 80 mm Hg.

MATERIALS AND METHODS

The study populations included 65 normotensives and 120 hypertensives attending the OPD of M. S. Ramaiah Hospitals and were willing to be part of the study. The inclusion criteria for the cases were clinically diagnosed prehypertensives and essential hypertensives without any complications. The study population having systolic B.P less than 120 mm of Hg and diastolic B.P less than 80 mm of Hg were categorised as normotensives, prehypertensives having systolic B.P between 120 to 139 mm Hg or diastolic B.P between 80 to 89 mm of Hg and essential hypertensives having systolic B.P greater than equal to 140 mm of Hg or diastolic B.P greater than equal to 90 mm of Hg or treated with antihypertensives. The exclusion criteria for the study included secondary hypertension, diastolic blood pressure >110 mm Hg on drug therapy, diabetes mellitus, serum creatinine concentration > 2.2 mg/dl, body mass index (BMI) > 34 kg/m^2, pregnancy, malignancy, stroke and myocardial infarction. The demographic details and anthropometric measurements were collected. The blood pressure was measured by using a mercury sphygmomanometer. About 5 ml of blood is collected in a BD gel vacutainer and allowed to clot. The serum was separated from the sample at the earliest after centrifugation and serum creatinine was estimated by alkaline picrate method. Estimation of GFR - eGFR (estimated Glomerular Filtration Rate) was calculated by using MDRD (Modification of diet in renal disease) formula. eGFR ($mL/min/1.73\ m^2$) = 186 x (Plasma/serum creatinine mg/dL) $^{-1.154}$ x $(age)^{-0.203}$x (1.210 if black) x (0.742 if female)[7]. eGFR greater than $90ml/min/1.73\ m^2$ was considered to be normal.

Statistical analysis

The results are expressed as Mean ± SD. Significance was assessed at 5 % level of significance. Analysis of variance (ANOVA) was used to find the significance of study parameters and Pearson correlation was used to study the relation between the various parameters. Statistical analysis was performed using SPSS 15.0 software.

RESULTS

The results are analysed by dividing the study population into normotensives, prehypertensives and essential hypertensives

subgroups. The age distribution of the study population is shown in Table 1. In the study, prehypertension is observed more in the age group between 31-40 years and essential hypertension in the age group between 41-50 years as in table 1.

Table 1
Age distribution of study population

Age in years	Controls		Pre HTN		HTN	
	No	%	No	%	No	%
27-30	4	5.7	1	3.2	0	0.0
31-40	13	20.0	23	41.9	24	37.1
41-50	48	74.3	27	54.8	41	62.9
Total	65	100.0	50	100.0	65	100.0

Table 2
Gender distribution of controls and hypertensives.

Gender	Controls		Pre HTN		HTN	
	No	%	No	%	No	%
Male	28	43	34	68	32	49.2
Female	37	57	16	32	33	50.8
Total	65	100.0	50	100.0	65	100.0

In the study male prehypertensives are more as compared to female prehypertensives. But there is equal distribution of males and females with essential hypertension as shown in table 2.

Table 3
BMI (kg/m^2) of controls and hypertensives.

BMI(kg/m^2)	Controls		Pre HTN		HTN	
	No	%	No	%	No	%
<25	65	100.0	47	94	39	60.0
25-30	0	0.0	3	6	26	40.0
Total	65	100.0	50	100.0	65	100.0

In most of the prehypertensives and 60% of the essential hypertensives, the BMI is found to be less than 25 kg/m^2. Nearly 40% of the essential hypertensives have BMI greater than 25 kg/m^2 in the study (Table 3).

Table 4
Comparison of BMI & BSA in controls, prehypertensives and essential hypertensives.

	Controls	Pre HTN	HTN	P value
BMI kg/m^2	21.18±3.42	23.39±1.14	24.43±1.90	<0.001**
BSA m^2	1.72±0.09	1.66±0.13	1.70±0.11	0.099+

However a gradual increase in the BMI kg/m^2 is observed from controls to prehypertensives and essential hypertensive cases as shown in table 4. A significant increase in systolic B.P, diastolic B.P and mean arterial pressure are observed in essential hypertensives. Prehypertensives have higher systolic and diastolic BP as compared to controls as shown in table 5.

Table 5
Comparison of SBP (mm Hg), DBP (mm Hg) & MAP (mm Hg) in controls, prehypertensives and essential hypertensives.

	Controls	Pre HTN	HTN	P value
SBP (mm Hg)	114.86±2.84	131.16±5.60	153.26±7.96	<0.001**
DBP (mm Hg)	72.63±5.46	83.74±3.00	92.51±6.88	<0.001**
MAP (mm Hg)	86.49±3.64	99.53±2.71	112.71±4.80	<0.001**

Table 6
S. creatinine (mg/dl) and eGFR (ml/min/sq.m) in controls, prehypertensives and essential hypertensives.

	Controls	Pre HTN	HTN	P value
S .creatinine (mg/dl)	0.75±0.11	0.63±0.12	0.97±0.11	<0.001**
eGFR (ml/min/sq.m)	103.4±10.45	140.00±15.82	79.06±7.08	<0.001**

There is a significant decrease in S. creatinine in prehypertensives as compared to controls. However a significant rise in eGFR is observed in prehypertensives as compared to controls (Table 6). There is increase in S. creatinine but within physiological range in essential hypertensives as compared to controls. A decrease in GFR is observed in hypertensives as compared to controls and prehypertensives (Table 6).

Table 7
Pearson correlation of eGFR (ml/min) between other parameters in prehypertensives and essential hypertensives.

Pearson correlation	Pre HTN		HTN	
	r value	P value	r value	P value
eGFR (ml/min) vs BMI(kg/m^2)	0.337	0.064+	-0.376	0.026*
eGFR (ml/min) vs BSA (m^2)	-0.046	0.806	0.072	0.680
eGFR (ml/min) vs SBP (mm Hg)	0.395	0.028*	-0.025	0.885
eGFR (ml/min) vs DBP (mm Hg)	0.018	0.922	-0.026	0.882
eGFR (ml/min) vs MAP (mm Hg)	0.297	0.105	-0.036	0.835
eGFR (ml/min) vs S. creatinine (mg/dl)	-0.624	<0.001**	-0.104	0.554

But all hypertensives in the study have eGFR greater than 60 ml/min. There is a significant negative correlation between eGFR (ml/min) and BMI (kg/m^2) indicating in essential hypertensives there is associated increase in BMI and decrease in eGFR. However, there is only statistically significant correlation between BMI and eGFR in prehypertensives. A significant positive correlation is observed between systolic B.P and eGFR in prehypertension. The correlation between S. creatinine and eGFR is highly significant with p<0.001 in prehypertensives (Table 7).

Table 8
Cut off value of eGFR in prehypertensives and essential hypertensives.

eGFR	Cut-off score	Sensitivity	Specificity	AUC	SE	P value	Remarks
Pre-HTN	>116	96.77	97.14	0.982	0.018	<0.001**	Excellent test
HTN	≤86	91.43	91.43	0.967	0.022	<0.001**	Excellent test

ROC curve was plotted with a cut off value of eGFR greater than 116 ml/min in prehypertensives and eGFR less than equal to 86 ml/min in essential hypertensives. In prehypertensives using a cut off level of eGFR at 116 ml/min, the sensitivity and specificity are found to be more than 96% and the area under ROC curve is about 0.982 and has been found to be a reliable parameter to be

assayed in preHTN in the study (Table 8). At eGFR cut off level of less than equal to 86 ml/min, the sensitivity and specificity was found greater than 91% and the area under ROC curve was found to be about 0.967 in the study (Fig 1, 2).

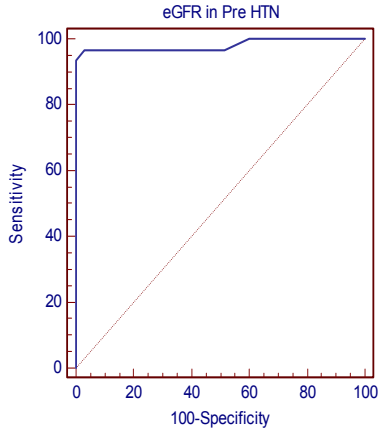

Figure 1
ROC curve of eGFR in prehypertensives. At eGFR of >116ml/min, the area under curve is about 0.982.

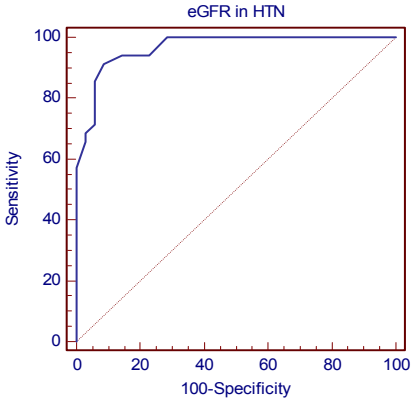

Figure 2
ROC curve of eGFR in essential hypertensives. At eGFR of ≤ 86ml/min, the area under curve is about 0.967.

Table 9
The distribution of prehypertensives with regards to eGFR (ml/min).

eGFR	Pre HTN	
	No	%
90-119 ml/min	5	10
120-139 ml/min	21	42
>140 ml/min	24	48
Total no of cases	50	100.0

Nearly 90 % of the prehypertensives are found to have glomerular filtration rate greater than 120 ml/min (Table 9).

Table 10
The distribution of hypertensive cases with regards to eGFR.

eGFR	HTN	
	No	%
65-75 ml/min	14	28
76-85 ml/min	28	56
86-95 ml/min	8	16
Total no of cases	50	100.0

56% of essential hypertensives have GFR between 76-85 ml/min and only 28% have GFR between 65 - 75 ml/min. 84% of essential hypertensives have GFR greater than 60ml/min and less than 86 ml/min (Table 10).

DISCUSSION

High arterial pressure is a marker of impending renal dysfunction. Essential hypertension is found to be associated with a functional defect in sodium chloride excretion and renal vasoconstriction[8]. Under physiological condition there is balanced release of relaxing and contracting factors by endothelial cells that can modulate vascular smooth muscle tone and contribute to the pathophysiology of hypertension. eGFR calculation based on S. creatinine is found to be more reliable and cost effective parameter to assess GFR. In the study glomerular filtration rate is found to be increased in prehypertensives as compared to hypertensives and normotensives. In preHTN there are pertinent changes in renal hemodynamics including increase in glomerular filtration due to associated cardiovascular reactivity[9]. Glomerular hyperfiltration is an indicator of the early stages of renal dysfunction in essential hypertension. Long standing increase in glomerular filtration can initiate the process of renal dysfunction[10]. Schmieder et.al.[11] have reported glomerular hyperfiltration due to sympathetic activation in early stages of essential hypertension and is mediated via post glomerular vasoconstriction. Hyperfiltration can be due to afferent arteriole dilatation. Brenner et.al.[12] have reported it can also be due to elevated glomerular hydraulic pressure in hypertension. Elevated blood pressure predisposes in the initial stage to rise in glomerular capillary hydraulic pressure and increase glomerular filtration[13]. Renal hemodynamics has been found to play a vital role in the development and maintenance of arterial hypertension. The study shows a progressive decline in glomerular filtration rate from preHTN to HTN along with the rise in systolic arterial pressure. Sympathetic nervous system activation leads to increased renal arteriole vasoconstriction leading to reduced renal perfusion. Progressive decrease in GFR is matched by a reciprocal increase in arterial pressure which helps to maintain sodium balance and body fluid homeostasis[14]. The cause for the increase in GFR is not very clear. NO may be involved in increase of glomerular filtration rate[15]. Nitric oxide can exert a decisive role in the regulation of arterial pressure by influencing vascular tone in the cardiovascular system and serves as a mediator of the changes induced by the arterial pressure in tubular sodium reabsorption. Glomerular hyperfiltration initiates a cycle of progressive increases in intraglomerular pressure and repetitive renal injury[16, 1]. Brenner and colleagues[16] have proposed that a congenital reduction in the number of nephrons plays an etiologic role in hypertension, via elevation of glomerular filtration rates in the residual nephrons followed by a deleterious cycle of elevated intraglomerular pressures and glomerular injury. Glomerular hyperfiltration in the initial stages of essential hypertension may also be mediated by angiotensin II[11]. An increase in preglomerular resistance occurs in hypertension. Due to variation in mean arterial pressure among prehypertensives and

essential hypertensives as in the study, has the potential to modify glomerular filtration rate by directly influencing the glomerular capillary hydrostatic pressure. In the study, the decline in glomerular filtration has been found in hypertensives which can be due to increase in glomerular hydraulic pressure due to inappropriate afferent arteriole dilation. eGFR reduction in hypertensives induces endothelial dysfunction establishing a cyclical process which not treated promotes the progression of both renal and vascular damage[17]. There is a decrease in renal plasma flow with the progression of hypertension. Guyton et al[18] have reported kidney to regulate blood pressure via sodium homeostasis. Semplicini et al[19] have reported increased proximal tubule Na^+ reabsorption contributes to the pathophysiology of glomerular hyperfiltration in patients with essential hypertension, and is compensated by increased atrial naturitic peptide levels. There is a defect in renal sodium excretion at normal perfusion pressure (abnormal pressure natriuresis) in hypertension. Prolonged glomerular hyperfiltration can result in progressive glomerular sclerosis there by ensuing kidney failure after over a period of time**.** It has been postulated that glomerular hyperfiltration and endothelial dysfunction are early features of essential hypertension that may predispose to elevation of blood pressure[20]. In the study a significant negative correlation is found between GFR and S. creatinine in prehypertensives indicating the decrease in S. creatinine level can be due to increase in GFR thereby increasing the filtration fraction of serum creatinine. The area under the curve shows high sensitivity and high specificity for GFR indicating the significance of measurement of glomerular filtration rate is more relevant than estimating S. creatinine which is within physiological limit in most of pre hypertensives and essential hypertensives. The progression of CKD is best assessed by sequential measurement of glomerular filtration rate[21]. As nearly 90 % of the prehypertensives had GFR greater than 120 ml/min and 84% of the essential hypertensives had GFR less than 86 ml/min. Hence estimating serum creatinine and further measuring GFR would provide a better indicator of ongoing pathophysiological changes in the renal system in these cases rather than measuring only their blood pressure. The study shows that treatment of prehypertensives is also imperative as these individuals are at increased risk of progression to established essential hypertension furthermore would reduce cardiovascular risk as well as risk of renal dysfunction.

CONCLUSION

As per the JNC 7 report on Prevention, Detection Evaluation and treatment of high blood pressure, blood pressure should be treated in all individuals having B.P >130/80 mm Hg . Hence identifying individuals who are at increased risk among prehypertensives by measuring their glomerular filtration rate may be more beneficial rather than only measuring S. creatinine level which may not very suggestive. However, additional studies needs to be carried out on a larger sample size along with better indicators of alteration in glomerular filtration are needed to substantiate these findings.

ACKNOWLEDGMENT

The authors wish to acknowledge the Indian Council of Medical Research for selecting and approving this project under STS 2013 Program. The encouragement by M. S. Ramaiah medical college scientific research committee is duly acknowledged. We also thank Dr. Vasudha KC, Professor and Head, Department of Biochemistry, M S Ramaiah Medical College, Bangalore for her inspiration and encouragement.

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