Int J Pharm Bio Sci 2013 Jan; 4(1): (P) 1 - 8

Research Article **Pharmacology**

International Journal of Pharma and Bio Sciences

ISSN 0975-6299

A COMPARISON OF EGFR USING SERUM CREATININE AND CYSTATIN FOR THE ASSESSMENT OF RENAL INVOLVEMENT IN HYPERTENSION.

JITHESH TK*[1], RIJU MATHEW[2], JAYAPAL. V[3] AND VIJAYAKUMAR. T[4]

1. *Assistant professor, Department of Biochemistry MES Medical College, Perinthalmanna*
2. *Research fellow, Yenapoya university, Mangalore*
3. *Chairman, Hrithyalaya institute of preventive cardiology, Trivandrum.*
4. *Head, Basic medical sciences, Educare institute of dental sciences, Kottakkal*

ABSTRACT

A study was conducted to evaluate the usefulness of GFR to assess the renal involvement in hypertension. GFR was assessed using the conventional blood urea and serum creatinine values and the eGFR is calculated based on serum creatinine by using the MDRD formula and Cockcroft – Gault formula. The values obtained were compared with serum Cystatin C and Cystatin based eGFR. It was observed that even though serum creatinine based eGFR is a good marker for renal assessment this method is lacks sensitivity and cannot be applied in GFR blind area. Cystatin C , Cystatin C based eGFR were found to be more reliable and sensitive than the earlier markers particularly in areas were the decrease in GFR is marginal. Hence it is suggested that Cystatin C and Cystatin C based eGFR are better markers for the assessment of renal involvement in hypertension.

KEY WORDS : Hypertension, Chronic Kidney Disease, End Stage Renal Disease, Glomerular Filtration Rate, Creatinine clearance, Cystatin C, Estimated GFR

JITHESH TK
Assistant professor, Department of Biochemistry MES Medical College, Perinthalmanna

Corresponding author

INTRODUCTION

Hypertension (HT) is one of the most common worldwide diseases affecting humans. Epidemiological studies show a steadily increasing trend in the prevalence over the last 40 years, more in urban than in rural population. In a study in Kerala, the awareness, treatment, and adequacy of control of hypertension was 39%, 29%, and 10%, respectively, in the urban elderly population.[1] The systemic arterial pressure and morbidity appears to be quantitative rather than qualitative as the risk to an individual patient may correlate with the severity of hypertension. HT puts stress on several organs called target organ including kidneys, eyes and heart causing them to deteriorate over time. It can lead to complications in other parts of the body because of the damage to the blood vessels and excessive pressure on the arterial walls can damage vital organs. It remains silent, being generally asymptomatic during its clinical course. As it is hidden beneath an outwardly asymptomatic appearance, the disease does immense harm to the body in the form of target organ damage; hence the WHO has named it the silent killer[2]. HT causes renal disease and renal complications. Hypertensive nephropathy is a medical condition referring to damage to the kidney due to chronic high blood pressure. In advanced stages renal failure occurs. Chronic kidney disease (CKD) is the progressive loss in renal function over a period of months or years. In most forms of CKD glomerular filtration rate tends to be decreased inexorably once a certain threshold of nephron destruction has occurred. While CKD is more common among women, men with CKD are 50% more likely than women to progress to kidney failure.[3] The progressive decrease in glomerular filtration rate accompanied by glomerulosclerosis and interstitial fibrosis leads to progressive replacement of nephrons by extracellular matrix. The measurement of GFR is extensively used for the diagnosis and prognosis of CKD.

Renal hypertension puts stress and increased pressure on the kidney, and is a major cause of end stage renal disease (ESRD) in the elderly. The attention is being paid globally to CKD is attributable to the increased prevalence and its role in increasing the risk of cardiovascular disease. Therefore prevention, early detection, and intervention are the only cost effective strategies. Prevention of ESRD by early detection and treatment is of importantance to stop the growing need for dialysis and renal transplantation. The progression of CKD to ESRD is mediated by several risk factors acting alone or in combination. [4] In most forms of CKD glomerular filtration (GFR) tends to decrease progressively once a certain threshold of nephron destruction has occurred. The progression of CKD is best assessed by sequential measurement of glomerular filtration rate. GFR is used for the diagnosis and prognosis of CKD and is measured on the basis of estimation of GFR using different formulas. GFR can be estimated by measuring the clearance of certain substances excreted by the kidney. Creatinine and urea are the conventional markers used for the measurement of GFR. The laboratory marker that has long served as the mainstay for detecting impaired kidney function is serum creatinine (SCr). These GFR based on creatinine measurements are unable to detect decline in renal function in the creatinine blind GFR area. The limitations of SCras a measure of GFR have led to an extensive search for a more sensitive laboratory marker of impaired renal function. Several new biomarkers like Cystatin C (CysC) and beta trace protein were introduced for GFR estimation as alternate markers to creatinine. Cystatin C, a cysteine protease inhibitor produced by nucleated cells, has received most attention.[5] It is a good marker of renal function and correlates better to direct measures of GFR more precisely than creatinine, because its serum concentrations

are independent of muscle mass and do not seem to be affected by age or sex.[6] Studies on eGFR based on CysC are scanty and often inconclusive. Very few attempts were made earlier to evaluate advantages of eGFR based on CysC over the eGFR calculated on SCr. Hence the present study was undertaken to comparethe efficacy of eGFR using serum creatinine and cystatin for the assessment of renal involvement in hypertension.

MATERIALS AND METHODS

The study was conducted at Educare Institute of Dental Sciences, Kottakkal, MES Academy of Medical Science, Perinthalmanna and Hrithayalaya institute for preventive cardiolgy, Trivandrum, Kerala. One hundred and twenty clinically proved patients below the age of 65 years formed the test group. The control group consisted of 60 subjects selected from the siblings, teaching and nonteaching staff of the institutes. Detailed clinical, epidemiological and anthropometric characteristics were recorded using proforma. Five ml of fasting venous blood and a random urine sample were collected from all the subjects after getting the informed consent, as per the criteria laid down by the Institutional Ethics Committee. Serum was separated immediately after clotting and the following investigations were carried out.

1. Serumcreatinine by Jaffe's reaction.
2. Serum CysC by particle-enhanced turbidimetric assay.[7]
3. Estimated GFR based on creatinine (eGFR) was calculated by using modification of diet in l disease (MDRD) formula and Cockcroft – Gault formula.[8], [9]
4. Estimated GFR based on CysC was calculated using three different equations.[10]

All results were expressed as mean ± SD. Independent sample't' test was performed using SPSS for comparing various risk/biomarkers, biochemical and genetic characteristics. Correlations of parameter were analysed using Karl Pearson correlation coefficient.[11] Probability values of $p < 0.05$ were considered to be statistically significant.

RESULTS

There were 180 subjects in the present study out of which 120 formed the test group and the remaining were age and sex matched control. The male to female ratio of the test and control group were 57: 43. The mean age of the study population was 57.41± 10.12 years while that of the control population were 48.6%. The result of the present study is given in Table 1. Comparison of the mean values of the biochemical parameters of the test group with that of the control showed significant variations.

Table 1
Group Statistics

				t-test for Equality of	
	Category	**N**	**Mean ± SD**	**t**	**Sig. (2-tailed)**
BP Systolic	Control	60	111.65 ± 7.46	-13.311	.000
	Test	120	154.00 ± 24.04		
BP Diastolic	Control	60	74.43 ± 4.55	-10.299	.000
	Test	120	92.74 ± 13.37		
CystatinC	Control	60	0.69 ± 0.18	-9.307	.000
	Test	120	1.99 ± 1.07		
Creatinine	Control	60	0.95 ± 0.31		

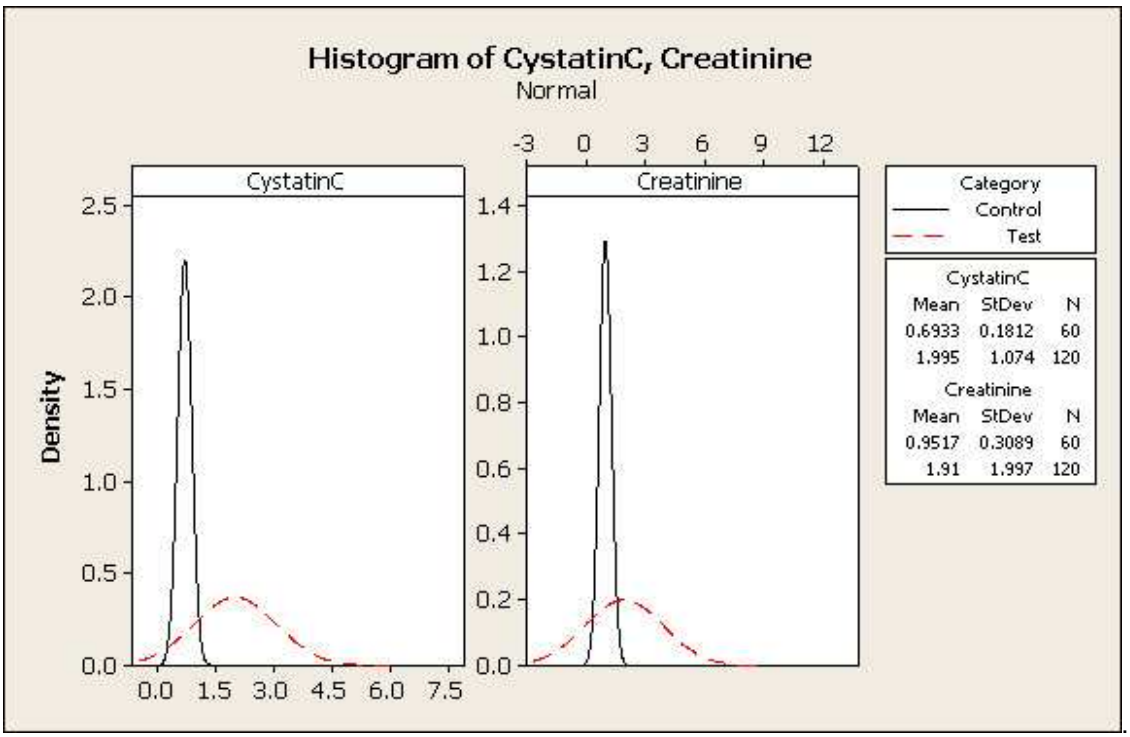
	Test	120	1.91± 2.00	-3.690	.000
eGFR MDRD	Control	60	115.15 ± 59.29		
	Test	120	59.37 ± 31.11	8.287	.000
eGFR CysC	Control	60	130.68 ± 45.20		
	Test	120	41.63 ± 17.55	18.954	.000
eGFR CG	Control	60	104.48 ± 34.59		
	Test	120	56.35 ± 28.04	10.025	.000
eGFR CysC - Age	Control	60	130.28 ± 42.59		
	Test	120	39.76 ± 16.39	20.491	.000
eGFR Cys Cr	Control	60	113.18 ± 39.31		
	Test	120	43.28 ± 17.81	16.426	.000

Serum CysC level in test population was 1.99 ± 1.07 and that of control group was 0.69 ± 0.18. The student t test was done, which showed significant ($p<0.001$) increase in hypertensive patients. The mean SCrlevel was 1.99 ± 1.07, which was above the normal level. The correlation between SCysC and SCr is shown in table 2 and figure 1.

Table 2

Correlations of CysCvs.Creatinine		
		Creatinine
CystatinC	Pearson Correlation	.559**
	Sig. (2-tailed)	.000
	N	180
*****. Correlation is significant at the 0.01 level (2-tailed).***		

Figure 1

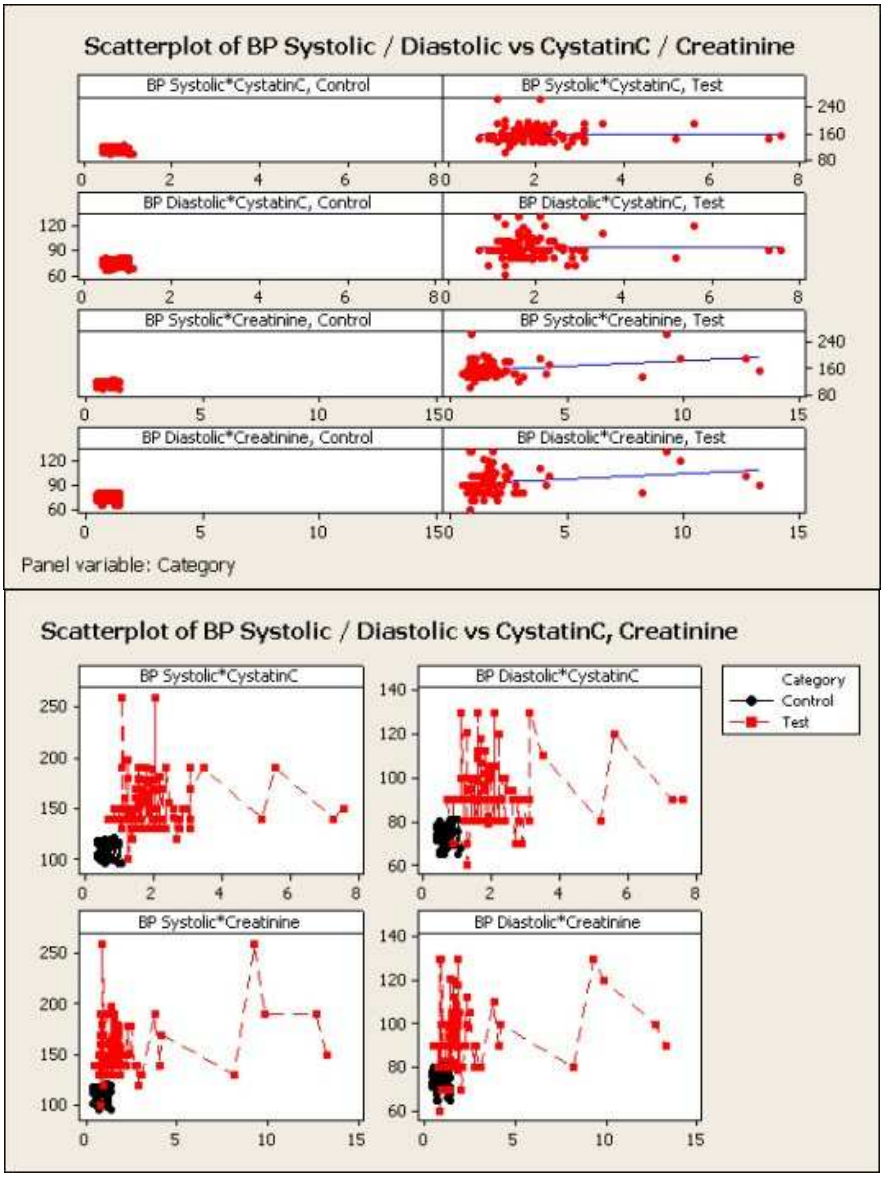


There was a significant correlation between SCysCwith systolic and diastolic blood pressure (P=0.000) and SCr with systolic and diastolic blood pressure (P=0.000) (shown in table 3 and figure 2).

Table 3
Correlation of SCr and CysC with BP

		Creatinine	CystatinC
BP Systolic	Pearson Correlation	.371**	.412**
	Sig. (2-tailed)	.000	.000
	N	180	180
BP Diastolic	Pearson Correlation	.324**	.357**
	Sig. (2-tailed)	.000	.000
	N	180	180

Figure 2
Correlation of SCr and SCysC with BP

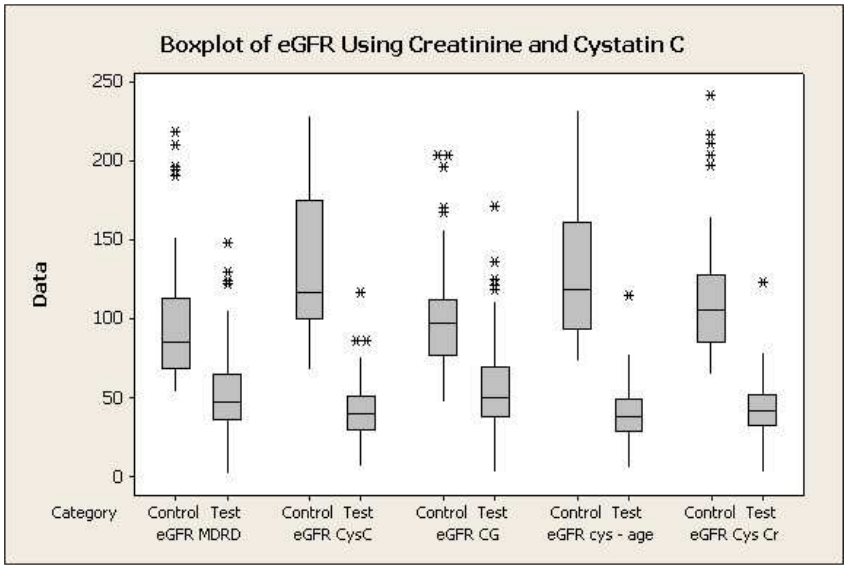


The eGFR using SCris calculated using MDRD equation and the value was 59.37 ± 31.11 for test group and 115.15 ± 59.29 for control group. Test population showed a significant decrease in eGFR (p value < 0.05). The eGFR using cystatin was calculated using 3 different equations and correlation between these equations are presented in table 4 and figure 3.

Table 4
Correlations between the eGFR Equations

		Creatinine Based eGFR		Cystatin C based eGFR		
		eGFR MDRD	**eGFR CG**	**eGFR CysC**	**eGFR CysC - Age**	**eGFR Cys Cr**
eGFR MDRD	Pearson Correlation		0.919**	0.685**	0.669**	0.876**
	Sig. (2-tailed)		0.000	0.000	0.000	0.000
eGFR CysC	Pearson Correlation	0.685**	0.666**		0.996**	0.923**
	Sig. (2-tailed)	0.000	0.000		0.000	0.000
eGFR CG	Pearson Correlation	0.919**		0.666**	0.673**	0.872**
	Sig. (2-tailed)	0.000		0.000	0.000	0.000
eGFR CysC - Age	Pearson Correlation	0.669**	0.673**	0.996**		0.926**
	Sig. (2-tailed)	0.000	0.000	0.000		0.000
eGFR Cys Cr	Pearson Correlation	0.876**	0.872**	0.923**	0.926**	
	Sig. (2-tailed)	0.000	0.000	0.000	0.000	
	N	180	180	180	180	180

Figure3
Correlations between the eGFR Equations



DISCUSSION

Hypertension is one of the major public health problems because of its high morbidity and mortality arising from the concomitant risks of cardiovascular and kidney disease. Given the high prevalence of hypertension in the population and the wide range of end organ damage associated with hypertension, it would be useful to quantitative the impact of hypertension with renal complication[12]. Renal disease is symptomless in its early phases and hence laboratory diagnosis by estimating GFR, is essential. SCr and urea are depend on variables like age, muscle mass and hence estimated GFR (eGFR) is used to assess the renal function. Estimated GFR cannot be used as a gold standard as it is only a calculated parameter based on variables especially serum creatinine which shows a blind area even when the GFR falls up to 50 % of normal. In this study SCr and SCysC were estimated and the values obtained were used for the calculation of eGFR. Estimated GFR is calculated using several prediction equations namely MDRD formula, Cockcroft – Gault formula, Jellifee formula and Gates formula.Out of these formulas, MDRD formula showed greater accuracy than other formulas. As Serum creatinine is insensitive to early reduction in creatinine blind area.

CysC and CysC based equations were used to calculate eGFR and found to be the most sensitive marker.[13] In the present study, eGFR calculated by both parameters showed significant decrease in the test group compared to the control group. The eGFR using CysC was better comparable with conventional markers. Even a mild reduction in GFR could be detected using CysC and that these were better indicators of deteriorating renal function, and thus allowing the possibility of taking preventive action. Our finding is well in agreement of the previous workers who reported CysC as a better indicator for calculation of eGFR.[14,15]. Recently Waad - Allah etal [16] showed that eGFR based on SCr is a reliable and cost effective parameter to assess GFR and CysC may be a better marker for kidney injury and can be used for the diagnosis and management of renal disease. CysC seems to be excellent marker of renal function and available evidence demonstrates that SCysC is superior to serum creatinine as a marker of GFR, particularly in identifying small decreases in GFR.[17] The present study clearly indicate that both CysC and CysC based eGFR are more sensitive and reliable for assessing renal function, particularly in identifying small changes in GFR, than any other parameter at present in use. A great deal has already accomplished in establishing a role for routine SCysC determination in many clinical situations. Hence it is suggested that Cystatin C and Cystatin C based eGFR are better markers for the assessment of renal involvement in hypertension.

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