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Cystatin C: An Important Biomarker for Evaluating Early Renal Dysfunction in the Hypertensive Patients of Kolkata, West Bengal

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Abstarct: Background: Hypertension has been recognized as one of the causes of Chronic Kidney Disease as it contributes to 40% of all CKD cases. Cr and eGFR calculated from creatinine based equation has been in practice for diagnosis and treatment of CKD for ages. Cystatin C, a polypeptide synthesized by all nucleated cells has been found to play a major role in detection of early renal impairment in hypertensive nephropathy patients. Objective: To compare the role of serum creatinine and cystatin C in diagnosing early CKD. Method: A total of 88 hypertensive patients and 70 controls were enrolled in the study. HTN patients were grouped as Stage I and Stage II on the basis of their blood pressure. eGFR was calculated by different equations based on estimated serum creatinine and cystatin C. Results: The serum creatinine, cystatin C and blood pressure of the subjects were observed to be much higher in both stage I and stage II hypertensives as compared to their controls (cr: 1.29±0.56 &1.54±0.91 vs 0.72±0.13; cysC: 1.42±0.82 &1.98±1.02 vs 0.76±0.21; SBP: 142.33±13.2 & 167.57±8.5 vs 128.89±14.1). Cystatin C showed more positive correlation with SBP (r= 0.323; p=0.0092) than creatinine (r=0.1068; p=0.3617 [NS]). An inverse association of eGFR with both creatinine and cysC was found in the hypertensive in comparison to their peer normotensives (58±17.6 & 54.48±25.32 vs 107.41±19.14). But cysC based eGFR was much reduced than creatinine based one thus indicating its importance in early detection of CKD. Conclusion: Serum cystatin C was proved to be a better predictor of CKD than creatinine among hypertensive patients.

Keywords: Cystatin C, Hypertension, Renal Marker, Creatinine, eGFR

1. Introduction

Hypertension has been attributed to be a leading cause of various life threatening diseases primarily involving cardiovascular and renal diseases. It seriously imposes a global burden in the developing as well as in the developed countries due to its increased prevalence in last few decades [1]. In United States of America more than 50 millions of people are affected with adult hypertension [2]. Hypertension is considered to be responsible for 10% of all deaths in Indian scenario and it has been anticipated that India will have 213 million hypertensive in 2025. Notable effects of hypertension in chronic kidney disease patients have been reported in numerous observational studies [3-5] as it is found to be an essential component in developing CKD, a worldwide epidemic in recent time. Cystatin C plays a major role in hypertensive nephropathy and bears a close correlation with mild to moderate reduction in glomerular filtration rate in these patients. Role of cys C has been studied in the hypertensive patients of different ethnic origins including Blacks, African –American, nonhispanics, Whites and Chinese [6]. Most of the CKD patients associated with hypertension are detected at last stage of CKD due to the asymptomatic nature of hypertension and seemingly normal serum creatinine level for a prolonged period of time until > 50% loss of nephrons has occurred. Cystatin C is paid a global attention due to its unique ability to detect renal dysfunction at earlier stage which might prevent the adverse cardiovascular outcome in CKD patients [7].

Shipak et al, observed that the raised level of cystatin C less than 1 mg/dl was associated with the adverse outcome of

cardiovascular diseases and at four fold higher risk to advance in to CKD as compared to the subjects with normal cystatin C [3]. It is a well known fact that most of the CKD patients die due to cardiovascular accidents rather than advancing in to end stage renal diseases. Cystatin C is proved to be reliable marker for stroke, heart failure and coronary artery diseases in addition to its role in renal diseases [8].

Creatinine based GFR, a worldwide accepted endogenous renal marker for decades has now been put in to question because of its insensitivity to diagnose early renal impairment. On the other hand cystatin C has emerged to be a better GFR marker due to its good performance over creatinine as it remains unaffected by age, sex, muscle mass, diet.

The importance of cystatin C based GFR in hypertensive patients has not been exclusively studied in Eastern Indian population so far in spite of its immense importance in early prediction of renal dysfunction [6]. This study is aimed to evaluate the effectiveness of cysC with decreased renal function in hypertensive patients.

2. Subject

This study was performed in the Department of Biochemistry, in collaboration with Department of Medicine at Ramakrishna Mission Seva Pratishthan Hospital, Kolkata. 200 patients were recruited in this study who attended Medicine OPD of the hospital in the period of July 2016 to May 2017. Informed consent was obtained from all subjects who participated in the study as per ICMJE (International Committee of Medical Journal Editors) recommendations.

3. Method

The study group comprised of 88 patients with newly diagnosed with hypertension according to Joint National Committee on prevention, detection, evaluation and treatment of high blood pressure (JNC7) [1]. Patients with severe cardiac or renal insufficiency, diabetes mellitus, chronic kidney disease, malnutrition, thyroid disorders, pregnancy and on steroid therapy were excluded from this study.

Detailed patient histories including demographic characteristics and anthropometric measurements, medication, concomitant illness, duration of hypertension were meticulously recorded. Seventy age and sex matched normotensive healthy subjects (BP ≤ 120/80 mm of Hg) were included as controls. The hypertensive patients were divided into two groups HTN I and HTN II depending on their systolic and diastolic pressure according to JNC 7 crteria [1] (Table 1: JNC7 criteria)

Table 1. *JNC7 criteria.*

Blood Pressure Classification	Systolic (mmHg)	Diastolic (mmHg)	Normal
<120	<80 Pre-hypertension	120-139	80-89
Stage I Hypertension	140-159	90-99	_
Stage II Hypertension	≥ 160	≥100	_

Creatinine (sarcocine oxidase) and cystatin C (latex turbidometry), were measured both in case and control subjects by auto-analyzer vitros 4600 (Ortho Clinical Diagnostics, JNJ) and RA-50 semi auto analyzer respectively. The reference ranges for creatinine (Male: 0.8-1.25 mg/dl; Female: 0.7-1.04 mg/dl) and Cystatin C (0.57-1.05 mg/l) were considered for this study.

Ethical clearance was obtained from Institutional Ethical Committee of RKMSP. Estimated GFR (eGFR) was computed by creatinine calculator using MDRD (Modification of diet in renal diseases) equation and CKD-EPI cystatin C calculators alone or in combination with creatinine and cystatin C.

4. Results

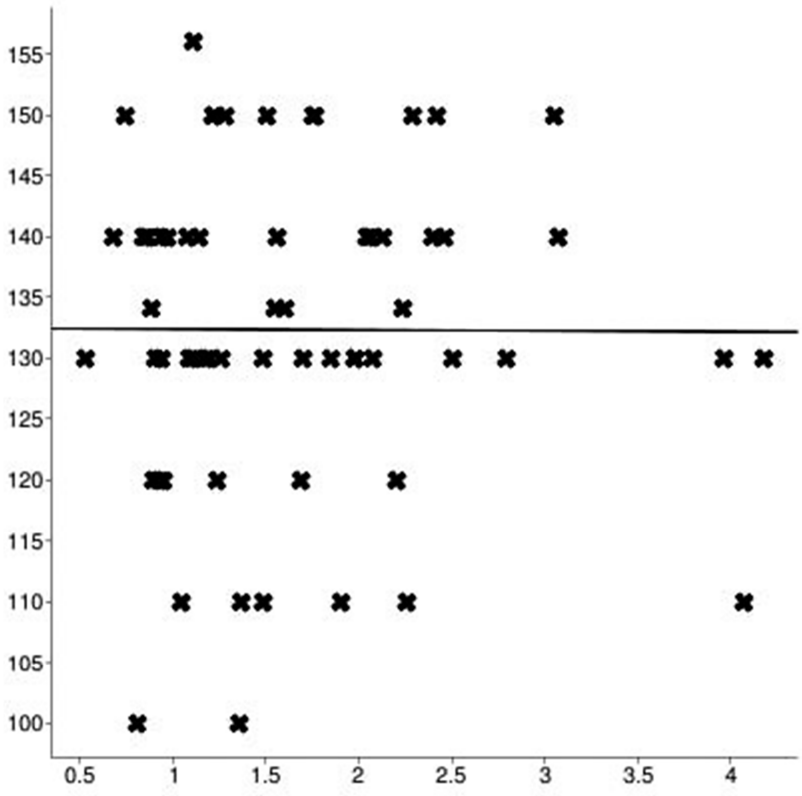
Eighty eight hypertensive patients and seventy control subjects were participated in this current study. Out of 88 patients sixty four patients had HTN I [142.33±13.2/97.05±9.87] and twenty four patients had HTN II [167.57±8.5/105.65±14.08]. Both the groups showed significantly elevated systolic and diastolic pressure as compared to their control group [128.89±14.1/80.54±10.58; ($p<0.0001$)]. Most of the hypertensive patients were within the age group of 20-80 years with a mean age of 58.83±15.17 in HTN I and 53.82±11.34 in the HTN II categories. Among the total patients 64 were male and 24 were female and the male female ratio was 8:3. Mean creatinine in HTN I group was 1.29±0.56 whereas it was observed to be more elevated in the patients with HTN II 1.54±0.91. Significantly raised creatinine was observed in hypertensive patients as compared to the normotensive controls [0.72±0.13] ($p<0.0001$) Serum Cystatin C level was significantly raised in hypertensive patients with respect to their peer control group (1.42±0.82 for HTN I and 1.98±1.02 for HTNII vs 0.76±0.21) respectively. As expected there was a significant reduction of creatinine based eGFR (MDRD) in both hypertensive groups (HTN I & HTNII) in comparison to their controls (58±17.6 & 54.48±25.32 vs 107.41±19.14). This reduction of eGFR was more obvious in the hypertensives using cystatin C based equations as compared to the cr-based equation which is quite evident from their eGFR values [58±17.6 vs 54.06±28.5 in the HTNI and 54.48±25.32 vs 50.91±24.45. in the HTN II subjects]. The decrease of eGFR using cystatin C equation was 4-5ml/min less than creatinine based equation [Table 2].

Table 2. *Biochemical and Clinical characteristics in Control and patients with HTNI and HTNII.*

Parameter (Mean values)	Control N =70	Stage I HTN N=64	P value	Stage II HTN N = 24	P value
Age	52.39 ±13.4	58.82±11.34	0.0055	53.83±15.17	0.687 (NS)
BMI	23.93±3.21	23.09±3.66	0.1761 (NS)	25.41±4.87	0.1791 (NS)
Systolic Blood Pressure	128.89±14.1	142.33±13.2	0.164 (NS)	167.57±8.5	<0.0001
Diastolic Blood Pressure	80.54±10.58	97.05±9.87	0.0603 (NS)	105.65±14.08	<0.0001
Creatinine	0.72±0.13	1.29±0.56	<0.0001	1.54±0.91	<0.0001
Cystatin C	0.76±0.21	1.42±0.82	<0.0001	1.98±1.02	<0.0001
eGFR MDRD	107.41±19.14	58±17.6	<0.0001	54.48±25.32	<0.0001
eGFR Cystatin C eq.	108.35±23.86	54.06±28.5	<0.0001	50.91±24.45	<0.0001

*Correlation significant at p value <0.05; NS= Non Significant at p<0.05

Both group of hypertensives showed positive correlation between systolic blood pressure and serum Cystatin C (r=0.323; p=0.0092 Figure 1) than creatinine (r=0.1068; p value non significant) although the relationship between diastolic pressure and cystatin C was found to be non significant in them [Table 3]



X axis: Cystatin C; Y axis: Systolic Blood Pressure

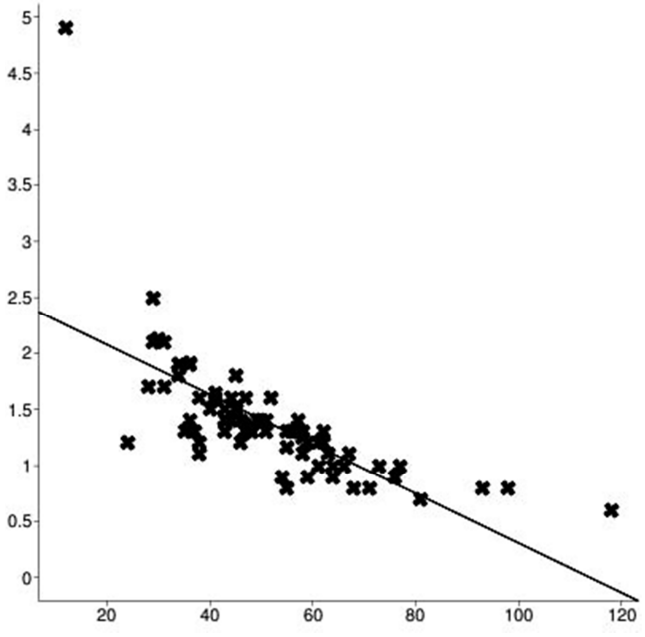
Figure 1. *Cystatin C vs Systolic blood pressure in HTN patients.*

Table 3. *Correlation study between biochemical and physiological parameters: A Comparison in Control & Hypertensive patients.*

Parameters	Groups	r value	p value
Systolic Blood Pressure VS Creatinine	Control	0.1563	0.410
	HTN	0.1068	0.3617 (NS)
Systolic Blood Pressure VS Cystatin C	Control	0.1815	0.33716
	HTN	0.323	0.0092
Diastolic Pressure VS Cystatin C	Control	0.12	0.322 (NS)
	HTN	0.0523	0.628 (NS)
Creatinine VS Cystatin C	Control	0.505	0.004424
	HTN	0.4429	0.002
Creatinine VS eGFR MDRD eq.	Control	-0.37	0.039443
	HTN	-0.6952	<0.0001
Cystatin C VS eGFR Cystatin C eq.	Control	-0.8958	<0.0001
	HTN	-0.8371	<0.0001

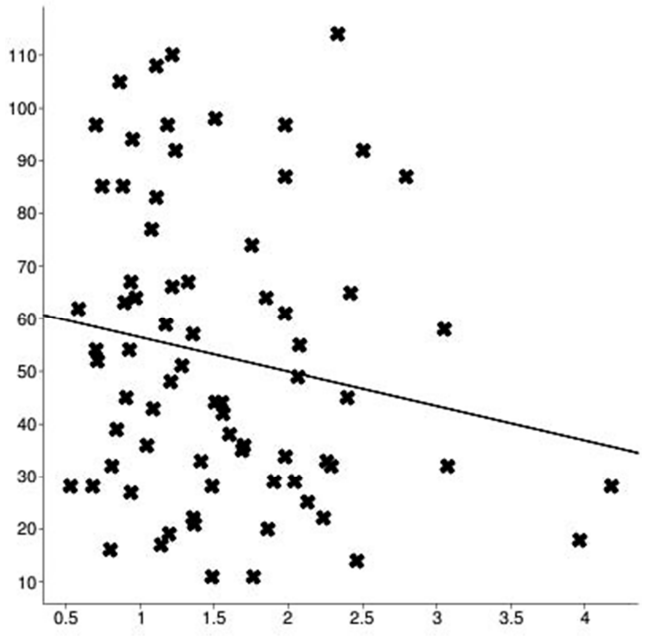
*Correlation significant P value <0.05; NS= Non Significant at p<0.05

Correlation of cysC with eGFR was found to be better than creatinine as evidenced by their r value [r= -0.83 vs -0.69, p<0.0001; Figure 2, Figure 3] thus supporting the role of Cystatin C as a better renal marker than creatinine in the hypertensive patients of Kolkata, West Bengal.



X axis: eGFR (ml/min); Y axis: Creatinine (mg/dl)

Figure 2. *Correlation between Creatinine and eGFR in HTN patients.*



X axis: Cystatin C; Y axis: eGFR

Figure 3. *Correlation between Cystatin C and eGFR in HTN patients.*

5. Discussion

Chronic kidney disease (CKD) takes a lead among all non-communicable diseases in India. An increasing trend of prevalence of hypertension, obesity, diabetes and cardiovascular diseases among the Indians are noticed in last few decades [9] and exercises a tremendous threat on Indian economy.

A close link of obesity, cardiovascular diseases and chronic kidney disease with hypertension has been deciphered in recent studies [10, 11]. 7.6 million deaths are already been reported due to high blood pressure across the world and majority of them died either cardiovascular diseases or stroke [15, 16, 17]. A spike of cardiovascular diseases is of growing concern in modern India due to uncontrolled explosion of HTN, dyslipidemia, diabetes and other life style disorders in recent years and it will be the major cause of death in coming years [12]. Epidemiological studies revealed that one third of adult Indians is reported to be hypertensive. North-East India showed a strikingly elevated percentage (44%) of HTN among the elderly persons. Prevalence of hypertensives in South India is also worrisome (21%). A high leap of prevalence is also observed in Eastern and Western part of India with 31.7% and 18% respectively than previous years [13, 14, 15]. Hypertension was observed to be moderately less in rural India (12-17%) than its urban counterpart (20-40%). The most shocking part in Indian perspective is that most of the hypertensives in rural India are unaware of their hypertensive status and the deadly outcome of the disease. The same picture is also reflected in urban section of the society. The detrimental role of hypertension in the underlying pathology of chronic kidney disease has now been highlighted due to the alarming increase of incidence of CKD in hypertensive patients. Two major determinants of CKD, hypertension and diabetes are being recognized all over the world including India for decades. The sharp increase of the prevalence of CKD in India in last few years was observed to be associated with the high rise of diabetes and hypertension among young and middle aged Indians [16]. The inhabitants of Kolkata mainly Bengalese also experience the same fate with enormous prevalence of kidney diseases in the city due to rampant increase of obesity, diabetes and hypertension in the adolescents, young and middle aged persons [17]. Lack of physical activity, stressful life, and unhealthy food habits are the main accused for developing metabolic syndrome, diabetes, dyslipidemia, hypertension in young Bengali population.

Our study indicated a significant negative correlation of serum cystatin C with e-GFR in essential hypertensive patients of Kolkata, West Bengal who are at high risk to develop chronic kidney disease. This is the first observational study assessing the role of cystatin C in mild or moderate decrease of GFR in the Bengali hypertensives which has not been reported earlier. Hypertensive people who seemed to be asymptomatic with any major complaints visited the medicine OPD for a regular check up showed high levels of serum cystatin C but with moderate increase of serum creatinine. Cystatin C based EGFR showed that the patients with hypertension already developed CKD with decreased

eGFR (<60 ml/min) of which they were completely unaware. These groups of people were hardly concerned of their poor status of kidney which required immediate medical intervention. In this study, raised serum Cystatin C revealed renal damage in the hypertensive patients who showed seemingly normal or moderately elevated serum creatinine which is in accordance with numerous studies across the globe [18, 19].

6. Conclusion

It is high time to quantitiate the profound impact of systolic blood pressure on kidney dysfunction in the hypertensive patients. Initiative should be taken to incorporate serum cys C as a part of routine investigations required for the diagnosis of pre clinical kidney damage in the hypertensive and diabetic people who are at high risk to develop CKD. Moderately reduced renal function in middle aged patients should not be overlooked in order to prevent further advancement leading to develop chronic kidney disease. Cystatin C based GFR will be helpful to prevent delayed diagnosis of renal diseases and untimely death of many young individuals due to this. Adequate measures and rigorous follow up could avoid renal complications and associated cardiovascular events in the CKD patients. Cystatin C based study will surely set up a new bench mark in the diagnosis and therapeutics of chronic kidney disease in coming years.

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