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Study of Relationship between Kidney Function and Systolic Blood Pressure: New Insights from Cystatin C

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Abstract

Background: Control of hypertension is of utmost importance in treating chronic kidney disease (CKD). The relationship between renal function and blood pressure (BP) components has been studied in persons with diagnosed CKD, diabetes or hypertension. Whether renal function in such cases is associated with systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse pressure is unclear.

Methods: In the study we have evaluated the association between renal function test parameters and each BP component using cystatin C in 80 essential hypertensive patients and 80 age and sex matched normotensive healthy controls.

Results: We observed that cystatin C showed significant positive correlation with SBP in both stage I ($p<0.05$ and r value 0.36) and stage II ($p<0.00001$ and r value 0.66) hypertensive patients. However cystatin C didn't show any significant correlation with DBP.

Conclusion: As SBP was significantly associated with kidney function across a wide range of cystatin C concentrations, even in subjects with presumably normal kidney function, this can provide a vital link in diagnosis of worsening of renal function at an early stage. For control of hypertension in patients undertaking anti-hypertensive medications this can also serve as an important marker.

Keywords: Cystatin C; SBP; DBP; Essential Hypertension; Renal impairment

Abbreviations: ACE: Angiotensin Converting Enzyme; Ang II: Angiotensin II; BMI: Body Mass Index; BP: Blood Pressure; CAD: Coronary Artery Disease; CHD: Coronary Heart Disease; CHF: Congestive Heart Failure; CI: Confidence Interval; CSF: Cerebrospinal Fluid; CVD: Cardiovascular Disease; DBP: Diastolic Blood Pressure; EDRF: Endothelium Derived Relaxing Factor; eGFR: Estimated Glomerular Filtration Rate; ESRD: End Stage Renal Disease; GFR: Glomerular Filtration Rate; HDLc: High Density Lipoprotein Cholesterol; H_2O_2: Hydrogen Peroxide; JNC: Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure; LCAT: Lecithin Cholesterol Acyl Transferase; LDLc: Low Density Lipoprotein Cholesterol; MDRD: Modification of Diet in Renal Disease; MOH: Ministry of Health; NO: Nitric Oxide; ROS: Reactive Oxygen Species; SBP: Systolic Blood Pressure; SD: Standard Deviation; TC: Total Cholesterol; TG: Triglyceride; TGF-β: Transforming Growth Factor β; UK: United Kingdom; US: United States; VCAM-1: Vascular Cell Adhesion Molecule-1; VLDLc: Very Low Density Lipoprotein Cholesterol; VSMC: Vascular Smooth Muscle Cell; WHO: World Health Oraginsation.

Introduction

In developing countries like India, hypertension is the leading non-communicable disease and is estimated to be attributable for nearly 10 percent of all deaths [1]. Adult hypertension prevalence is increasing rapidly in both rural as well as in urban population [2,3]. The number of hypertensive individuals is anticipated to nearly double from 118 million in 2000 to 213 million in 2025[3].

A classification proposed by The Joint National Committee VII (JNC-VII) on Prevention, Detection, Evaluation, and Treatment of high Blood Pressure in the year 2003 has defined a blood pressure of less than 140/90 mm of Hg as acceptable, beyond which is considered as hypertension. It recommends blood pressure criteria for defining normal blood pressure, prehypertension, hypertension (stages I and II), and isolated systolic hypertension, which is a common occurrence among the elderly [4].

Even moderate elevation of arterial blood pressure is associated with a shortened life expectancy. Dietary and lifestyle changes can improve blood pressure control and decrease the risk of associated health complications, although drug treatment is often necessary in some people.

Hypertension doubles the risk of cardiovascular diseases, including coronary heart disease, congestive heart failure, ischemic and hemorrhagic stroke, renal failure, and peripheral arterial disease [5].

Hypertension is a risk factor for renal injury and End Stage Renal Disease. The atherosclerotic, hypertension related vascular lesions lead to glomerular injury ultimately leading to glomerulosclerosis and ischemic and atrophic changes to renal tubules. In malignant hypertension there is fibrinoid necrosis of the afferent arterioles, sometimes extending to glomerulus ultimately leading to decreased renal function. When renal function decreases, the serum concentration of many low-molecular weight proteins increases. As a consequence, the blood levels of some small proteins, such as lysozyme, β2-microglobulin and cystatin C, have been proposed as indices of renal function [6,7].

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Recent studies have found strong association between renal function and pulse pressure in elderly persons with isolated systolic hypertension [8-13]. Another study found that SBP was a stronger predictor of increase in serum creatinine than DBP, pulse pressure or mean arterial pressure in an elderly population with isolated systolic hypertension [14]. Although SBP, DBP and pulse pressure are known to suggest cardiovascular risk, their relative association with renal function test parameters were not known previously.

So it is of utmost importance to find out a correlation between degrees of hypertension, the serum cystatin C to find its implications in the treatment of hypertension, as mildly reduced renal function may be an underappreciated barrier in the achievement of BP targets.

Materials and Methods

The study was conducted in the Department of Biochemistry, in collaboration with Department of Medicine, S.C.B. Medical College and Hospital, Cuttack from September 2013 to December 2014. The sample size was 160, consisting of 80 cases and 80 controls. The study has been approved by institutional ethical committee and informed written consent was taken from both cases and controls.

80 patients of age group 25-65 years, attending Out Patient Department and indoor in the Department of Medicine, S.C.B. Medical College and Hospital, Cuttack were included in the study. Patients with newly diagnosed Essential Hypertension were selected and diagnosed on the basis of their history, physical examination, biochemical investigations and according to the JNC 7 (Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure) Criteria for the diagnosis of hypertension[4].

The control group includes 80 ages and sex matched normotensive (BP ≤ 120/80 mm Hg) healthy adults with normal serum lipid profile, no symptoms and signs suggestive of hypertension and no family history of the disease. The controls were selected from the department staffs and students after through medical examination, serial BP measurements and detailed history taking.

Three ml of blood was collected after overnight fasting of 8 hours from all enrolled patients and healthy controls for the assessment of lipid profile, creatinine, cystatin-C levels. Demographic characteristics (name, age, sex), history of risk factors (smoking, family history, medications, alcohol intake etc.), systolic and diastolic blood pressures, were recorded in detail.

The inclusion criteria were as follows: Adults aged 25 years and above diagnosed with hypertension according to JNC 7 (Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure).

The exclusion criteria included Secondary hypertension categories (Endocrine hypertension, renal or renovascular, related to collagen vascular disease, aortic coarctation, etc), Diabetes mellitus, Hypertensive retinopathy and/or nephropathy, Chronic kidney disease, Previous history of corticosteroid/cyclosporine use.

Cystatin C was measured by turbidimetric immunoassay method [15]. Statistical analysis was done using SPSS and Microsoft Excel 10.

Results

In our study the age of patients and healthy controls ranged from 25 yrs. to 65 yrs (Table 1). In the study group, maximum number of hypertensive patients were within the age group of 51-60 yrs. Out of the 80 hypertensive patients,41 were males and 39 were females. Out of the 41 male patients, 22 were stage 2 hypertensives and out of the 39 female patients, 22 were stage 2 hypertensive cases.

Age group (In Yrs.)	Control Group (n =80)			Study Group (n=80)					
				Stage I Hypertension			Stage II Hypertension		
	M	F	Total	M	F	Total	M	F	Total
<30 yrs	11	3	14	2	2	4	1	0	1
31-40 yrs	10	20	30	2	2	4	0	2	2
41-50 yrs	10	9	19	6	4	10	5	9	14
51-60 yrs	7	6	13	6	7	13	14	10	24
>60 yrs	3	1	4	3	2	5	2	1	3
Total	41	39	80	19	17	36	22	22	44

Table 1: Shows the age, sex distribution of essential hypertension cases and healthy individuals. Majority of stage I and stage II hypertension patients were in the age group of 51-60 yrs.

Sl. No.	Parameter (mg/dl)	Control group (n=80)	Study group (n=80)	
			Stage 1 hypertensive (n=36)	Stage 2 hypertensive (n=44)
		Mean ± SD	Mean ± SD	Mean ± SD
1.	Total Cholesterol	144.33 ± 29.33	182.25 ± 44.75**	182.86 ± 49.35**
2.	Triglycerides	97.5 ± 25.12	132.97 ± 63.90**	169.93 ± 63.98**
3.	HDLc	44.57 ± 7.84	44.33 ± 8.28	44.11 ± 8.49
4.	LDLc	79.92 ± 23.87	105.75 ± 36.97**	107.94 ± 41.99**
5.	VLDLc	19.68 ± 4.96	26.75 ± 12.83**	33.77 ± 12.94**

Statistically significant **p<0.0001, as compared to control

Table 2: shows the lipid profile parameters. Serum total cholesterol, triglycerides, LDLc, VLDLc were found to be significantly raised and HDLc level was not found to be significant when compared with controls.

Most of the patients having hypertension (both male and females) belong to higher age group. It is due to decrease in arterial compliance in major arteries due to atherosclerosis. In females this may be also due to the hormonal changes that occur during menopause. The decline in the estrogen/androgen ratio dilutes the vasorelaxant effects of estrogens on the vessel wall and promotes the production of vasoconstrictive factors such as endothelin and also causes an up regulation of the ''Renin Angiotensin System" with an increase in plasma-renin activity.

In this study the mean age of stage 1 hypertensives was 48.97 ± 10.91 years, stage 2 hypertensives was 53.86 ± 7.43 years and of healthy individuals was 41.27 ± 10.86 years. Of the lipid parameters in hypertensive cases and control, a significantly higher level of total cholesterol was found in stage 1 and 2 hypertensives with a mean of 182.25 ± 44.75 mg/dl and 182.86 ± 49.35mg/dl respectively when compared to healthy controls (p<0.0001). Serum triglyceride was 132.97 ± 63.90mg/dl in stage 1 hypertensives and 169.93 ± 63.98mg/dl in stage 2 hypertensives. It was significantly raised in hypertension cases as compared to control (97.5 ± 25.12 mg/dl). (Table 2)

Mean serum LDLc was 105.75 ± 36.97 mg/dl in stage 1 hypertensive and 107.94 ± 41.99 mg/dl in stage 2 hypertensive and mean serum VLDLc was 26.75 ± 12.83mg/dl in stage 1 hypertensive and 33.77 ± 12.94 mg/dl in stage 2 hypertensives which when compared to controls, the raised value was found to be statistically significant (p<0.0001).

Mean serum HDLc was 44.33 ± 8.28 mg/dl in stage 1 hypertensives and 44.11 ± 8.49 mg/dl in stage 2 hypertensives which was not statistically significant when compared with controls (Table 2).

Hypertension and dyslipidemia are two of the main risk factors for vascular diseases which are often associated. The co-existence

of the two risk factors has more than an additive adverse impact on the vascular endothelium, which results in enhanced atherosclerosis, leading to target organ damage.

The exact mechanism by which a low HDL-c increases Cardio vascular disease risk has however not been fully elucidated, though experimental studies suggest a direct role for HDL-c in promoting reverse cholesterol transport from foam cells in the atherosclerotic plaque depots in blood vessels to the liver for excretion. HDL-c also exhibits potent anti-inflammatory and antioxidant effects that inhibit the atherogenic process.

Our study shows serum cystatin C levels were significantly increased ($p<0.0001$) in both stage I hypertensives (1.02 ± 0.23 mg/l) as well as stage II hypertensives (1.18 ± 0.25 mg/l) when compared with controls (0.82 ± 0.12 mg/l).

Jithesh et al. [16] have found that cystatin C levels were significantly increased ($p<0.001$) in hypertensive patients (1.99 ± 1.07 mg/l) when compared with controls (0.69 ± 0.18 mg/l).

Madhav Danthala et al., [17] have found that serum cystatin C levels were significantly raised in 62% (n=31) patients of acute ischaemic stroke compared with controls 14% (n=7) with a $p<0.001$.

Our study shows that serum cystatin C level showed significant positive correlation with systolic blood pressure (SBP) in stage I hypertensives (p value <0.05 and r value 0.36) as well as in stage II hypertensives (p value<0.00001 and r value 0.66).

Carmen Peralta et al., [14] have also found out that Systolic blood pressure and pulse pressure were significantly associated with kidney function across a wide range of cystatin C concentrations in hypertensive patients.

Our study shows that serum cystatin C level showed a positive correlation which is not significant with diastolic blood pressure (DBP) in stage I hypertensives (p value 0.16 and r value 0.24) as well as in stage II hypertensives (p value 0.10 and r value 0.25).

Carmen Peralta et al. [14] have also found that diasolic blood pressure did not show any association with cystatin C levels in hypertensive patients.

Koc et al., [18] have found that essential hypertensive patients taking anti hypertensives for 3 months had lower systolic blood pressure, diastolic blood pressure and cystatin C levels compared to pre-treatment levels.

The finding that kidney function is associated with SBP, not DBP warrants further exploration. Systolic hypertension and wide pulse pressure have been associated with vascular stiffness which may provide a clue to the association of kidney disease and cardiovascular disease. Although the target SBP for those with CKD is still uncertain, our study extends the findings of the strong association between kidney function and SBP.

By using a more sensitive marker (cystatin C) to determine kidney function, our analysis found an association of kidney function with SBP even in those with presumably normal renal function. This suggest the presence of factors that may affect the vasculature before clinical CKD is diagnosed, thereby providing new insight into the importance of the relationship between kidney function and SBP. Also as cystatin C shows significant positive correlation with SBP and creatinine does not, this also proves the superiority of cystatin C over creatinine as a marker for detecting renal impairment.

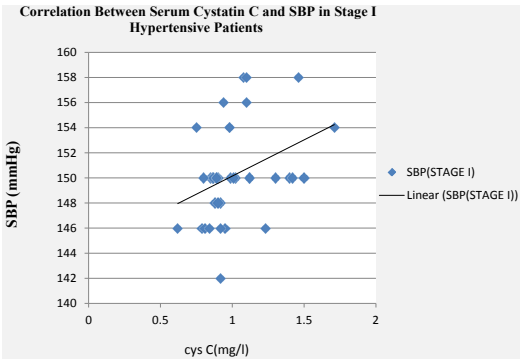

Figure 1: shows linear significant positive correlation between serum cystatin C & SBP in stage I hypertensive patients.

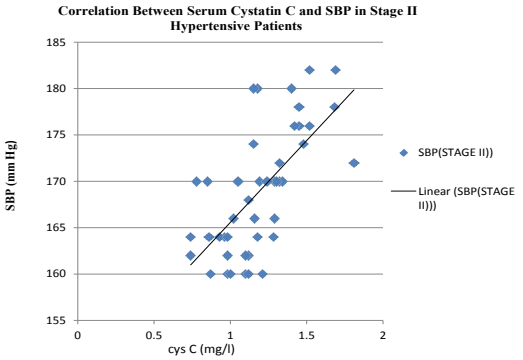

Figure 2: shows linear significant positive correlation between serum cystatin C and SBP in stage II hypertensive patients.

In our study we have selected only newly diagnosed essential hypertension patients, without treatment and at the end established a positive correlation between cystatin C with Systolic blood pressure. So it can further be established that patients who are under treatment, taking anti-hypertensives and thereby have controlled BP, have lower cystatin C levels. Thereby cystatin C can have important implications in the treatment part of hypertension.

Figure 1 shows a significant linear positive correlation between serum cystatin C and systolic blood pressure (r value 0.36 and p value <0.05) in stage 1 hypertensive patients.

Figure 2 shows a significant linear positive correlation between serum cystatin C and systolic blood pressure (r value 0.66 and p value <0.00001) in stage 2 hypertensive patients.

Progressively reduced kidney function is associated with higher mean SBP across the full range of kidney functions. With increase in SBP, cystatin C also increased linearly in both stage 1 and stage 2 hypertensive patients, with the association being more significant in stage 2 hypertensive patients.

Discussion

Our results showed a strong correlation between kidney function and SBP in the essential hypertensive patients throughout a wide range of kidney function levels. In contrast DBP showed no correlation with cystatin C levels. Also serum creatinine did not show any significant correlation when compared with SBP. Thereby our study proves that kidney function may be a more important determinant for adequate SBP control. Hereas lies the superiority of cystatin C over conventional renal function test parameters like creatinine.

The finding that renal function is associated only with SBP, not with DBP needs further explanation. Isolated systolic hypertension has long been found as a marker of cardiovascular risk [19,20]. Now high SBP has also been associated with vascular stiffness [21,22]. Creatinine level was only increased in stage 2 hypertensive patients when compared with controls. It also did not correlate with SBP. By using a more sensitive marker cystatin C [23-26] our study found a association between kidney function with SBP in essential hypertensive patients. It also showed a significant linear relationship between kidney functions with SBP (Figures 1 and 2) showing further importance in treatment of hypertension. Certain limitations were also there in our study. As ours is a cross sectional study, we cannot determine causality. We cannot determine the extent to which kidney dysfunction leads to elevated SBP or elevated SBP leads to kidney dysfunction. As our study also included the patients taking antihypertensives so BP level of them may be lower than those without treatment. However as the association between renal function and SBP persists despite this factor, it supports our hypothesis that mildly reduced renal function may be an underappreciated barrier for the control of hypertension. Our finding can be established further by including more number of cases as well as increasing the duration of study (Tables 3-8).

Category	Mean±SD	CI (Mean±2SE)	pvalue
Control(n=80)	0.82 ± 0.12	0.80 - 0.84	**<0.0001**
Cases (n=80)	1.11 ± O.25	1.07 - 1.15	

Table 3: shows mean serum cystatin C in controls to be 0.82 ± 0.12 mg/L (95% CI is 0.80-0.84 mg/L) where as in cases mean cystatin C(1.11 ± 0.25 mg/L) was found to be significantly raised (p<0.0001) with a 95% CI being 1.07-1.15 mg/L.

Sl. No.	Parameter (mg/dl)	Control group (n =80)	Study group (n=80)	
			Stage 1 hypertensive (n=36)	Stage 2 hypertensive (n=44)
		Mean ± SD	Mean ± SD	Mean ± SD
1.	Serum Urea	19.85 ± 7.69	35.61 ± 6.25**	40.52 ± 7.33**
2.	Serum Creatinine	1.01 ± 0.19	1.04 ± 0.18	1.18 ± 0.29*

*statistically significant (p< 0.001) as compared to control; **statistically significant (p< 0.0001) as compared to control

Table 4: shows the biochemical parameters in control group and study group.

Serum Cystatin C vs Systolic Blood Pressure(SBP)	r Value	p Value
Stage I Hypertension	0.36	<0.05
Stage II Hypertension	0.66	<0.00001

Table 5: shows the correlation study between serum cystatin C with systolic blood pressure(SBP). In stage I hypertensive patients a significant positive correlation was observed with a r value of 0.36 and p value <0.05. Stage II hypertensive patients also showed a significant positive correlation with r value of 0.66 and p value <0.00001.

Serum Creatinine vs Systolic Blood Pressure(SBP)	r Value	p Value
Stage I Hypertension	0.03	0.86
Stage II Hypertension	0.04	0.79

Table 6: shows the correlation study between serum creatinine with systolic blood pressure (SBP). In stage I hypertensive patients a non-significant positive correlation was observed with a r value of 0.03 and p value 0.86. Stage II hypertensive patients also showed a non-significant positive correlation with r value of 0.04 and p value 0.79.

Serum Cystatin C vs Diastolic Blood Pressure(DBP)	r Value	p Value
Stage I Hypertension	0.24	0.16
Stage II Hypertension	0.25	0.10

Table 7: shows the correlation study between serum cystatin C with diastolic blood pressure (DBP). In stage I hypertensive patients a non significant positive correlation was observed with a r value of 0.24 and p value 0.16. Stage II hypertensive patients also showed a positive correlation which is not significant (r value 0.25 and p value 0.10).

SL. No.	Parameter (mmHg)	Control group (n=80)	Study group(n=80)	
			Stage 1 hypertensive (n=36)	Stage 2 hypertensive (n=44)
		Mean ± SD	Mean ± SD	Mean ± SD
1.	SBP	116.2 ± 5.80	150.27 ± 3.82**	168.90 ± 6.77**
2.	DBP	75.57 ± 4.96	93.88 ± 2.66**	108.45 ± 5.92**

**Statistically significant (p <0.0001) as compared to control group. SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure

Table 8: shows the systolic and diastolic blood pressure in control and study group.

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