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Original Research Article

Estimation of Serum Creatinine and Cystatin C in Normotensive and Hypertensive Patients

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Abstract

Cystatin C is a cysteine proteinase inhibitor belonging to type 2 cystatin superfamily produced endogenously. The main catabolic site of cystatin C is Kidneys. It has been shown that cystatin C is a better marker of kidney dysfunction compared to creatinine. We in the present study tried to evaluate the cystatin C and creatinine levels in normal and hypertensive subjects and correlate the cystatin C levels with blood pressure and kidney functions in this group of the population. Methods: This prospective cross-sectional study was conducted in the Department of Biochemistry and General Medicine, Rajiv Gandhi Institute of Medical Sciences, Adilabad. A total of 105 patients were included in this study 56 patients were allotted to cystatin C group for estimation of cystatin C and 49 patients were allotted to creatinine group for estimation of creatinine levels. The results were arranged as quintile of cystatin C (Q1 – Q5) subgroups based on levels in cystatin C and similarly quintile of creatinine (Q1-Q5) in creatinine group. The coefficient of correlation 'r' values was estimated for cystatin C and creatinine with SBP and DBP. Results: Cystatin C levels of all the 5 sub-groups (Q1- Q5) the strong positive correlation was shown for SBP by Q4 with 'r' values +5.48 and Q5 with 'r' values +6.43 and DBP has positive correlation only in Q5 group value +0.44. Similarly, in the creatinine sub-groups, a positive correlation between SBP and creatinine levels found in Q4 and Q5 groups. The SBP in Q4 was with 'r' value +0.31 and Q5 was with +0.49 the values of DBP did not show a significant positive correlation with creatinine levels in all the groups. Conclusion: it can be concluded that cystatin C is a better marker of kidney functions and can be used to evaluate the blood pressure changes affecting the kidneys. However, the cystatin C test is costly and may not be feasible in low resource settings. In such cases, the continuance of the use of creatinine may be done for monitoring the kidney functions in hypertension.

Keywords: Cystatin C, Creatinine, Hypertension.

INTRODUCTION

Cystatin is a small protein was first isolated from chicken egg white has the ability to inhibit the activity of lysosomal cysteine proteinase [1]. A cysteine is thus a group of potent non-covalent competitive inhibitors of mammalian lysosomes. Cystatin C is a small 13kD protein which fulfills all the basic requirements of endogenous filtration [2]. The production of cystatin C is remarkably constant over the lifetime and its excretion from the circulation is complete via glomerular filtration. In the absence of significant tubular damage, cystatin C is reabsorbed and metabolized from the proximal tubular epithelium and not returned into the circulation [3]. Serum creatinine has been widely used in clinical practice as a standard marker of kidney functions. But serum creatinine levels are also affected by extrarenal factors such as the nutritional status of the individual and amount of muscle mass in the body [4]. Therefore creatinine levels have lower sensitivity for mildly reduced renal functions. Hence, the creatinine-based equations to estimate the GFR has been derived with the application of factors to compensate for nonrenal influences on the relationship between and GFR, but their precision, when applied to elderly patients, is unclear [5-7]. It has been shown that creatinine clearance overestimates GFR from 10-40% in healthy subjects and it is more unpredictable in patients with chronic kidney diseases [8]. There are also reports that intraday today CV for repeated measurements of creatinine clearance exceeds 25% [9]. Other studies have shown that cystatin C is superior and less affected by extrarenal factors than serum creatinine levels, therefore, cystatin C has emerged as a more accurate and sensitive marker of kidney functions compared to serum creatinine [10, 11]. There are also conflicting data regarding the GFR estimation by cystatin C and creatinine [2]. As renal

diseases are closely associated with cardiovascular diseases the prognostic value of cystatin C has been studied especially for the risk prediction of cardiovascular events and mortality [12-14]. With this background, we in the present study tried to evaluate the levels of cystatin C and creatinine in hypertensive patients and normotensive patients and find the correlation between the blood pressure readings and the levels of cystatin C and creatinine. The idea was to find which of the two was better correlated to blood pressure in this group of the population.

MATERIALS AND METHODS

This prospective cross-sectional study was conducted in the Department of Biochemistry and General Medicine, Rajiv Gandhi Institute of Medical Sciences, Adilabad. Institutional Ethical Committee permission was obtained for the study. Written consent was obtained from all the participants after explaining the nature of study in the local language. Those who were willing to participate were only included in the study. The inclusion criteria were OPD visitors of Department of General Medicine who were undergoing antihypertensive treatment and newly detected hypertensive patients. Randomly selected male and female subjects normal patients were included as controls; age group of all patients was between 30 to 60 years and those without significant comorbid conditions. Exclusion criteria were those not fitting in the inclusion criteria and those not willing to participate in the study and patients with significant renal dysfunctions Adilabad. A total of 105 patients were included in this study 56 patients were allotted to cystatin C group for estimation of cystatin C and 49 patients were allotted to creatinine group for estimation of creatinine levels. All the patients were estimated for anthropometric measurements and Blood pressure readings and blood sampling. The height of the subjects was measured with a stadiometer. The weight of measured in Kilograms and the BMI was calculated as Kg/m^2. Blood pressure was measured by the indirect method using a standardized mercury sphygmomanometer with optimal cuff size selected based on the subjects arm circumference. The cuff was tied to the right arm of the subject seated comfortably at rest for at least 5 minutes. The point of beginning of the appearance of Korotkoff's sound was taken as SBP and appearance of muffled sounds were taken as the DBP. All the measurements were performed by a single examiner in order to reduce inter-operator bias. The patient's history was recorded including a family history of hypertension and other diseases. A 10ml of blood sample was withdrawn from an antecubital vein in a vacutainer between 9:00 AM – 10:00 AM after overnight fasting of 8 hours. All the biochemical parameters were done with a fully automatic chemistry analyzer 'Beckman Coulter Au 400'. The serum cystatin C was measured with a latex turbidimetric immunoassay method. All the data was collected and analyzed using SPSS version 17 software on windows format.

RESULTS

A total of 56 patients were included in the study for cystatin C estimation. In this group out of 56 patients, 24 were known hypertensive and 32 were normotensive subjects. The results were divided in quintile of cystatin C levels. The lowest values were included in Q1 0.6 – 0.8 mg/L the total number of patients were 12 in this group. Out of which 8 were male and 4 female. The mean age of the patients in this group was 42.5 ± 5.0 years and based on the BMI 9 patients were with the normal weight and 3 patients were with overweight and the mean SBP in mmHg was 110 ± 5.6 and DBP was 82.2 ± 2.5 mmHg. The mean uric acid levels were 3.1 ± 1.25 mg/dl. The total cholesterol levels were found to be more than 240mg/dl in 2 patients and the mean FBS was 90.5 ± 6.5 mg/dl. The Q2 group levels were between 0.81 – 0.99 mg/L the total number of patients was 15 out of which 11 were male and 4 were female. The mean age group was 44.0 ± 3.25 years. Based on the BMI 9 patients were with the normal weight and 3 patients were with overweight and the mean SBP in mmHg was 110 ± 5.6 and DBP was 82.2 ± 2.5 mmHg. The mean uric acid levels were 3.1 ± 1.25 mg/dl. The total cholesterol levels were found to be more than 240mg/dl in 2 patients and the mean FBS was 99 ± 2.25 mg/dl. The Q3 group levels were between 1.0 -1.10 mg/L we found 10 patients in this group that included 7 male and 3 female patients. The mean SBP was 128 ± 8.8 mmHg and DBP was 90.6 ± 2.8 mmHg. The Q4 group levels were between 1.11 -1.29 mg/L we found 11 patients in this group that included 6 male and 5 female patients. The mean SBP was 132 ± 6.4 mmHg and DBP was 92.2 ± 2.4 mmHg. Similarly, the Q5 group levels were those with values of cystatin C > 1.29mg/L and 8 patients in this group that included 5 male and 3 female patients. The mean SBP was 142 ± 10.5 the mean 132 ± 6.4 mmHg and DBP was 95.6 ± 4.6 mmHg. The other variables are shown in Table 1. The Pearson coefficient of correlation 'r' was found for all sub-groups between the SBP, DBP and cystatin C levels of all the 5 sub-groups the strong positive correlation was shown by Q4 with 'r' values +5.48 and Q5 with 'r' values +6.43 for SBP and DBP has positive correlation only in Q5 group value +0.44.

Table-1: Showing the characteristics of the subjects involved in the study based on the quintile of cystatin C levels

Quintile of Cystatin C	Q1	Q2	Q3	Q4	Q5
	0.6 – 0.8 mg/L	0.81 – 0.99 mg/L	1.0 – 1.10 mg/L	1.11 – 1.29 mg/L	> 1.29 mg/L
Number of patients	12	15	10	11	8
M/F	8/4	11/4	7/3	6/5	5/3
Mean Age in years	42.5 ± 5.0	44.0 ± 3.25	48.5 ± 4.5	50.5 ± 1.5	55.5 ± 2.25
BMI in Kg/m^2					
< 25	9	7	2	3	1
25-30	3	5	5	6	3
> 30	0	3	3	2	4
Mean Systolic BP mmHg	110 ± 5.6	121 ± 4.4	128 ± 8.8	132 ± 6.4	142 ± 10.5
Mean Diastolic BP mmHg	82.2 ± 2.5	88.6 ± 3.6	90.6 ± 2.8	92.2 ± 2.4	95.6 ± 4.6
Mean Uric acid mg/dl	3.1 ± 1.25	3.2 ± 1.5	4.5 ± 2.6	6.5 ± 2.25	7.5 ± 4.5
Total Cholesterol mg/dl					
< 200 mg/dl	6	7	4	3	2
200 – 239 mg/dl	4	6	2	3	2
> 240 mg/dl	2	2	4	5	4
Mean Fasting Blood Sugar mg/dl	90.5 ± 6.5	99 ± 2.25	105.5 ± 1.5	111 ± 4.5	122 ± 5.5

A total of 49 patients who were normotensive and hypertensive were included in this group out of which 22 were known hypertensive and 27 were normotensive subjects and the results were arranged as per quintile of creatinine levels. The Q1 included those with 0.7 – 0.8 mg/dl. The mean SBP in this group was 114.0 ± 4.5 mmHg and DBP was 81.4 ± 2.5 mmHg. The numbers of patients were 10 in this group. All the patients in this group were normotensive subjects the mean FBS was 95.5 ± 3.5 mg/dl. The mean uric acid was 3.5 ± 1.25 mg/dl in this group. The second group Q2 was having the mean serum creatinine levels between 0.81 – 0.9 mg/dl. The mean SBP in this group was 122 ± 3.2 mmHg and the mean DBP in this group was 84.6 ± 3.2 mmHg. The mean serum uric acid levels were 3.3 ± 2.5 mg/dl and the mean FBS was 100± 2.25 mg/dl. The third group Q3 was with the range of creatinine between 0.91 – 1.0 mg/dl and SBP 128 ± 6.8 mmHg and DBP 91.2 ± 3.9 mmHg, the mean uric acid levels were 4.8 ± 3.1 mg/dl and mean Fasting blood sugar was 110.5 ± 1.5 mg/dl. The Q4 was with the mean creatinine levels of 1.1 – 1.2 mg/dl and SBP 134 ± 6.2 mmHg and DBP 93.4 ± 2.7 mmHg and the serum uric acid levels were 6.2 ± 1.2 mg/dl. The last group was with the serum creatinine levels > 1.21 mg/dl all the patients in this group were chronic hypertensive patients. The mean SBP was 144 ± 7.5 mmHg and the mean DBP was 93.4 ± 2.7 and the serum uric acid levels were 7.6 ± 3.5 mg/dl. The mean fasting blood sugar levels were 132 ± 2.5 mg/dl. Based on BMI it was found that 3 were obese and 1 was overweight and the other characteristics are given in table 2. The coefficient of correlation 'r' for this group was calculated it was found that there was a positive correlation between SBP and creatinine levels in Q4 and Q5 groups. The SBP in Q4 was with 'r' value +0.31 and Q5 was with +0.49 the values of DBP did not show a significant positive correlation with creatinine levels in all the groups.

Table-2: Showing the characteristics of the subjects involved in the study based on the quintile of Creatinine levels

Quintile of Creatinine	Q1	Q2	Q3	Q4	Q5
	0.7 – 0.8 mg/d	0.81 – 0.9 mg/dl	0.91 – 1.0 mg/dl	1.1 – 1.2 mg/dl	> 1.21 mg/dl
Number of patients	10	15	12	8	4
Male/Female	5/5	9/6	7/5	6/4	3/1
Age in years	35.5 ± 6.5	36.5 ±10.5	42.5 ±4.0	45.5 ± 3.5	53.5 ±5.5
BMI in Kg/m^2					
< 25	8	11	6	1	0
25-30	1	3	3	6	1
> 30	1	1	3	1	3
Mean Systolic BP mmHg	114 ± 4.5	122 ± 3.2	128 ± 6.8	134 ± 6.2	144 ± 7.5
Mean Diastolic BP mmHg	81.4 ± 2.5	84.6 ± 3.2	91.2 ± 3.9	93.4 ± 2.7	96.2 ± 3.1
Mean Uric acid mg/dl	3.5 ± 1.25	3.3 ± 2.5	4.8 ± 3.1	6.2 ± 1.2	7.6 ± 3.5
Total Cholesterol mg/dl					
< 200 mg/dl	3	4	6	0	1
200 – 239 mg/dl	4	7	4	3	1
> 240 mg/dl	3	4	2	5	2
Mean Fasting Blood Sugar mg/dl	95.5 ± 3.5	100± 2.25	110.5 ± 1.5	121 ± 4.5	132 ± 2.5

DISCUSSION

We in the present study found a strong positive correlation between cystatin C levels and blood pressure in hypertensive patients. The creatinine levels are also positively correlated with SBP in hypertensive patients however the association was not strong. Recent studies have confirmed that the serum concentration of cystatin C is a good indicator of GFR and comparable to the serum concentration of creatinine [15-17]. Numerous previous studies have suggested that cystatin C is more sensitive than creatinine in the measurement of GFT [18, 19]. However, the clinical role of cystatin C measurement is not clarified till now. One of the early sign of undetected hypertension is a decrease in GFR in an otherwise healthy patient. Therefore the estimation of GFR is important for the clinical evaluation of the patient with hypertension. Further, it is known that a substance qualifies to an estimation of GFR if it is exclusively eliminated for via renal filtration. The cystatin C fulfills this requirement very well. Creatinine is secreted by renal tubules as well as it can be alternatively secreted by the renal tubules. This alternative pathway of elimination compensates for the decrease in GFR and may keep the creatinine level unchanged until GFR has declined to less than 60 ml/min/1.73 m^2. Therefore the creatinine levels are likely to increase only if the capacity of alternate tubular secretion is used to its full capacity [3]. In this cross-section observational study the risk for hypertension was found in the highest quintiles Q5 and Q4 of cystatin C and it was significantly more than then when compared to Q3 a similar observation was also seen in the creatinine group however the mean BP in creatinine group was slightly more than the cystatin C group. In a multi-Ethnic study on atherosclerosis by Kestenbaum *et al*., [20] showed elevated serum cystatin C levels were associated with an increased risk of hypertension but they did not observe the same association in the Asian population of their study. Toshiaki Otsuka *et al*., [21] in Japanese population found an increased association of hypertension in highest quintiles of cystatin C, an observation similar to our study they also concluded that serum cystatin C levels could predict the 4-year risk of hypertension in middle-aged Japanese male population. One of the pathophysiological mechanism that involves the development of hypertension is reduced kidney function causes a decrease in the ability of the kidneys to excrete sodium thereby increases the blood volume [22]. There is greater activation of RAS and sympathetic nervous system in subjects with reduced kidney functions in this way the reduced kidney functions cause elevation of blood pressure. Perkins *et al*., [23] in a 4-year longitudinal study evaluating the population for diabetes, have reported that serially measured, correlated better with renal function decrease, an assessment done by determining Iothalamate clearance, than did serum creatinine levels for estimated GFR. Shlipak *et al*., [24] have shown the value of using serum cystatin C levels to evaluate renal function and reported that the serum cystatin C levels >1.10mg/L were associated with two times risk of evolution to chronic kidney disease. A study by Lesley AI *et al*., [25] for estimation of GFR from cystatin C and creatinine found that the GFR estimated based on equations that use cystatin C as the sole filtration marker not more accurate than creatinine-based estimated probably due to unknown non-GFR determinants of cystatin C they may be similar to that those of affecting the creatinine. Micheal GS *et al*., [26] concluded that the use of cystatin C alone or in combination with creatinine strengthens the association between the eGFR and the risks of death and end-stage renal disease across the diverse populations.

CONCLUSION

Within the limitations of the present study, it can be concluded that cystatin C is a better marker of kidney functions as compared to creatinine and it can be used for to evaluate the blood pressure changes affecting kidneys. However, the cystatin C test is costly and may not be feasible in low resource settings. In such cases, the continuance of the use of creatinine may be done for monitoring the kidney functions in hypertension.

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