Relationship between Serum Creatinine, Cystatin-C and Creatinine Clearance in Chronic Kidney Disease

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ABSTRACT:- Recommendations for laboratory diagnosis and monitoring of chronic kidney disease (CKD) state the use of both serum creatinine and cystatin-C in various clinical situations. The relationship of these markers to estimated glomerular filtration rate (eGFR) is found to be different in different populations. In India the routine reporting of eGFR is yet to commence. Meanwhile, the utility of these two serum markers as indicators of GFR is being evaluated in this cross-sectional study on CKD patients. The correlation between serum creatinine and cystatin-C was moderate, and cystatin-C correlated better with creatinine clearance than serum creatinine. The difference in handling of creatinine in the proximal tubule could be the reason.

Keywords:– chronic kidney disease, creatinine clearance, creatinine, cystatin-C

I.   Introduction

Chronic kidney disease (CKD) is a public health problem, with adverse outcomes of kidney failure, cardiovascular disease, and premature death. Estimates of the glomerular filtration rate (GFR) may replace the measurement of serum creatinine as the primary tool for the assessment of kidney function [1]. The National Kidney Foundation of the US, through its Kidney Disease Quality Outcome Initiative (K/DOQI) and other National institutions, recommend glomerular filtration rate (GFR) estimates for the definition, classification, screening, and monitoring of CKD. Prediction equations for GFR based on serum creatinine values were chosen both for adults (Cockcroft-Gault [C-G] and Modification of Diet in Renal Disease [MDRD] study equations) and for children (Schwartz and Counahan-Barratt equations) [2].

Despite standardization of serum creatinine assays, GFR estimates remain relatively imprecise owing to variation in non-GFR determinants of serum creatinine [3]. Age, race and sex do not account for all variations leading to imprecision in estimated GFR values. Further, the variable determinants of serum creatinine may be affected in both acute and chronic illness [4]. Such imprecision can potentially result in the misclassification of patients with estimated GFR less than 60 ml per minute per 1.73 m^2 of body-surface area, as having chronic kidney disease, leading to unnecessary diagnostic and therapeutic interventions.

Cystatin-C, a non-glycosylated cationic low molecular weight protein (Mw 13,343 Da) is an inhibitor of cysteine proteinases. This protein is eliminated by glomerular filtration, reabsorbed and catabolized in proximal renal tubular cells without tubular secretion. Compared to creatinine, cystatin-C is less affected by age, sex and muscle mass. Cystatin-C is said to be better estimate of true renal function than plasma levels of creatinine or a creatinine-based estimated glomerular filtration rate (eGFR). However, cystatin-C is to some extent affected by non-renal factors such as diabetes, high C-reactive protein, high white cell blood count and low serum albumin levels which might affect estimated GFR when using cystatin-C[5].

Plasma Beta Trace Protein (BTP) concentration positively correlated with cystatin-C concentration. Both, plasma BTP and cystatin-C concentrations, positively correlated with parameters such as serum creatinine, blood urea nitrogen, age and pro–B-type natriuretic peptide, whereas both negatively correlated with estimated glomerular filtration rate (eGFR), serum albumin, and hemoglobin. Neither BTP nor cystatin-C indicated a worsening renal function during index hospitalization. Both BTP and cystatin-C were significant predictors of death or heart failure hospitalization, whereas serum creatinine, eGFR, and blood urea nitrogen were no longer significant. Importantly, in patients with eGFR < 60 ml/min, elevated concentrations of BTP and cystatin-C were associated with significantly higher risk of adverse clinical events [6].

Data from several studies in which both serum creatinine and serum cystatin-C were compared to a clearance method for estimating GFR, cystatin-C measurement correlates more closely with GFR than does serum creatinine measurement [7].

It has been unambiguously proven that creatinine varies with age, gender and body mass. But in the case of cystatin-C, there are conflicting views, some evidence supporting, and certain other evidence opposing the influence of age, gender and body mass on cystatin-C levels[8].

Performance of estimating equations compared to measure GFR varied across populations, probably reflecting demographic and clinical characteristics of the study populations and methods to measure GFR. The estimating equations performed best when applied to populations most similar to those used to develop each equation. Inclusion or exclusion of age and gender factors in cystatin-C based equations may partially explain differences observed in some populations. All estimating equations using either creatinine or cystatin-C had noticeable imprecision, which was improved by including both cystatin-C and creatinine in an equation [9]

There is still lack of evidence for the usefulness of serum renal markers- creatinine and cystatin-C to denote the glomerular filtration rate measured based on them, especially in the Indian population. Their role in patients with CKD is being evaluated in this study.

II.   Aims and Objectives

The study was conducted to find the relationship between-
1.   Serum creatinine and serum cystatin-C
2.   Serum creatinine and creatinine clearance
3.   Serum cystatin-C and creatinine clearance
4.   Serum urea and serum creatinine, and
5.   Serum urea and serum cystatin-C.

III.   Materials and Methods

The present cross-sectional study was undertaken with a total number of 50 known cases of CKD. Age group was 40-70. The following parameters were estimated: serum urea, creatinine, cystatin-C. Immunoturbidimetry was used to estimate serum cystatin-C. Other parameters were measured by standard methods. Creatinine clearance was estimated using the formula: *UV/P*. Statistical analysis was done using Microsoft excel 2007. The Pearson correlation was used to analyze the relationship between various parameters; *p*-value less than 0.05 was considered statistically significant.

IV.   Results and Discussion

The correlation of serum creatinine with serum cystatin-C and correlation of both parameters with creatinine clearance was analyzed. The correlation was also determined between serum urea and serum creatinine and cystatin-C respectively. Values are given as mean $\pm$ standard deviation. Serum creatinine and cystatin-C had mean values of 5.71mg/dl and 6.85mg/dl respectively. Pearson correlation coefficient *'r'* had a value of 0. 448 when serum creatinine and serum cystatin-C were compared, which shows a positive but moderate correlation. *'r'* value of -0.419 was obtained when serum creatinine was compared with creatinine clearance, whereas serum cystatin-C showed a better correlation (-0.880) with creatinine clearance. This signifies that serum cystatin-C is a better indicator of renal function, as estimation of creatinine clearance is indicative of GFR. Creatinine clearance correlates better with cystatin-C. Though serum creatinine production is unaffected, the lesser correlation of serum creatinine with creatinine clearance over cystatin-C may be due to the difference in proximal convoluted tubular secretion rate of creatinine. The results of the study compare with the previous studies[8] which state that serum cystatin-C is a better predictor of GFR. Hence the levels of serum cystatin-C may be used in clinical practice to monitor patients with CKD.

Strong correlation was observed between serum creatinine and cystatin-C in a study conducted in diabetic CKD patients, the latter less strongly affected by weight and muscle mass. The authors however, state that the pathogenesis of diabetic kidney disease is complex and multifactorial [10].

A study from India demonstrated that serum creatinine correlated well with eGFR than serum cystatin-C in CKD patients. In the age-group 41-59years in the same study, cystatin-C correlated better with eGFR than creatinine. Serum cystatin-C, but, correlated better with measured GFR in all the patients in the study [8].

When serum urea levels were compared with serum creatinine and cystatin-C in the present study, there was stronger positive correlation between serum urea and creatinine, than between serum urea and cystatin-C (*'r'* values of 0.723 and 0.382 respectively). As is known, serum urea and creatinine are products of body metabolism, whereas serum cystatin-C is the product of a constitutive housekeeping gene, its synthesis occurring at a steady state, the serum levels mainly affected by renal function. The effect of factors influencing cystatin-C levels that affect the rate of synthesis of the protein, such as thyroid status and the use of steroids are to be eliminated. Elevations in urea level occur with high protein intake, more so in CKD patients. Serum creatinine levels are affected by both non-renal physiological factors and analytical interferences in the methods used.

V. Conclusions

From the present study, it can be concluded that serum cystatin-C levels better reflect the GFR than serum creatinine. Values of cystatin-C in serum maybe used to evaluate renal function in routine clinical practice. Laboratory testing plays a key role in the early detection of CKD [7]. The better correlation of serum cystatin-C with GFR increases its utility in clinical practice. It is also recommended that eGFR may be used to monitor patients already diagnosed with CKD [11]. Serum cystatin-C may be helpful in these patients. Serum urea levels cannot be used to monitor renal function in CKD patients but may indicate non-renal influences including patient's diet which can be addressed for reducing symptoms of elevated toxic excretory products.

Table 1- Biochemical parameters- mean, standard deviation (SD), maximum and minimum values

Biochemical Parameter	(Mean ± SD)	Maximum	Minimum
Cystatin C (mg/dl)	6.85 ± 1.36	9.86	4.54
Creatinine (mg/dl)	5.71 ± 0.75	7.23	4.39
Creatinine Clearance (ml/min)	50.56 ± 5.63	61.40	39.10
Urea (mg/dl)	112.38 ± 13.20	151.10	89.10

Table 2- Correlation of biochemical parameters (Pearson 'r')

Biochemical Parameter	Pearson 'r'(Correlation coefficient)
Cystatin C vs Creatinine	0.448
Cystatin C vs Creatinine Clearance	-0.880
Creatinine vs Creatinine Clearance	-0.419
Urea vs Cystatin C	0.382
Urea vs Creatinine	0.723

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