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RESEARCH ARTICLE

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IS CYSTATIN C ESTIMATION A BETTER MARKER IN CHRONIC KIDNEY DISEASE PATIENTS?

Corresponding Author

R.KUMARESAN

Department of Clinical Research, Periyar Maniammai University, Vallam, Thanjavur- 613 403, India.

Co Authors

P.GIRI

Kidney Care, Tiruchirappalli- 620 018, India.

ABSTRACT

To determine whether serum cystatin C is a better marker of Glomerular Filtration Rate (GFR) when compared with serum creatinine in subjects with chronic kidney disease (CKD).106 patients with chronic kidney disease were enrolled in this study. They were categorized into 4 groups, based on GFR levels. GFR<15 ml/min/1.73m^2 (group1; n = 20), GFR: 16-29 ml/min/1.73m^2 (Group 2; n = 36), GFR: 30-59 ml/min/1.73m^2 (group 3; n = 38), and GFR: 60-89 ml/min/1.73m^2 (group 4; n = 12). In all the groups, cystatin C correlated well with iGFR [*P*=<0.0001(group2); *P*=0.0001(group3); *P*= 0.0027(group4)] than creatinine (*P*=0.0019; *P*= 0.0185; *P*=0.0272 respectively), but a significant correlation between cystatin C with iGFR (*P*= 0.0178) was seen, on the other hand no significant correlation between iGFR with creatinine (*P* = 0.2285) in group 1.Our results showed that serum cystatin C is potentially a better marker for detecting impaired renal function than serum creatinine.

KEYWORDS

Glomerular Filtration Rate, chronic kidney disease, ^{99m}Tc -DTPA, PENIA, cystatin C, creatinine.

INTRODUCTION

The need for a simple, accurate and rapid endogenous marker of GFR has been a major limiting factor in clinical nephrology practice and research. Determination of GFR by clearance methods is time consuming and labour intensive. Owing to the inaccuracies associated with these methods, the measurement of endogenous blood substances are used to estimate GFR in the common practice. Properties of an ideal endogenous blood substance to estimate GFR should include release into the blood stream at constant rate and free filtration by the glomerulus elimination via the kidneys.

Serum creatinine is the most commonly used filtration marker in clinical practice but its accuracy is significantly hampered by assay interference, unreliability of urine collection and the confounding influence of diet, age, gender and muscle mass[1] and there are several well – reported difficulties concerning its analysis [2, 3].

Cystatin C is a 122 – amino acid 13 kDa protein that is a member of the family proteinase inhibitors. It is the product of a "housekeeping" gene expressed in all nucleated cells and is produced at a constant rate[4]. Because of its small size and basic pH (9.0), cystatin C is freely filtered by glomerulus. Cystatin C does not return to the blood stream and is not secreted by renal tubules; it has been suggested to be "ideal" endogenous marker[5]. The early methods for the determination of serum cystatin C were based on immunoelectrophoresis and single radial immunodiffusion from 1994 to 1997; fully automated assays were developed including Particle-Enhanced Turbidimetric Immunoassay (PETIA) and Particle-Enhanced Nephelometric Immunoassay (PENIA) [6-8].

The aim of this study was to correlate the serum cystatin C and serum creatinine with isotopic GFR to establish the good renal marker.

MATERIALS AND METHODS

(i) Subjects

Serum samples were obtained from one hundred and six patients with chronic kidney disease. The age of the subjects ranged from 21 to 85 (82 males and 24 females) years (Table 1). The subjects were categorized into 4 groups based on iGFR levels according to NKF-K/DOQI staging classification of CKD. Group1 (end stage renal disease) GFR <15 ml/min/1.73m^2 (n = 20); group 2 (severe stage); GFR ranges 16-29 ml/min/1.73m^2 (n = 36); group 3 (moderate stage) GFR ranges 30-59 ml/min/1.73m^2 (n = 38) and group 4 (normal (or) mild stage) 60-89 ml/min/1.73m^2 (n = 12).

Table1

Overall laboratory data for participants with means and standard deviations (n = 106)

Parameters	Mean ± SD
Age (years)	50.1 ± 15.5
Weight (kg)	64.1 ± 13.3
Height (cm)	163 ± 8.8
iGFR (ml/min/1.73m^2)	33.52 ± 23.78
Serum cystatin C (mg/l)	2.99 ± 1.23
Serum creatinine (mg/dl)	3.39 ± 2.05

(ii) Methods

Serum cystatin C was measured using PENIA kit (Dade Behring, Marbug, GmbH, Germany). Serum creatinine was measured by the Jaffe's method, using semi-autoanalyser (Microlab 200, Merck, USA). Isotopic GFR was determined by using ^{99m}Tc-DTPA renal scan (E.cam gamma camera, Siemens medical solutions Pvt.Ltd.USA). Written consent was obtained from all the study participants.

(iii) Statistics

Statistical analyses were performed using Medcalc statistical software (Belgium). Values are given as mean ± standard deviation. Multiple regression was performed to assess the influence and the degrees of significance were analyzed by Pearson correlation.

RESULTS

A significant correlation between cystatin C with isotopic GFR (r = -0.5236; *P*=0.0178) than serum creatinine (r = -0.2819; *P*=0.2285) in group 1 (Table 2). Cystatin C correlated well with isotopic GFR in group 2 (r = -0.7731; *P*=<0.0001), group 3 (r= -0.6080; *P*=0.0001); and group 4 (r= -0.7820; *P*=0.0027) than serum creatinine in group 2 (r= -0.4995; *P*=0.0019), group3 (r= -0.3803; *P*=0.0185) and group 4 (r = -0.6329; *P* = 0.0272). Cystatin C did not correlated with age (r = 0.1552, *P*= 0.1121), height (r= 0.1629, *P*= 0.0951) and weight (r= 0.1849, *P*= 0.0977). The sensitivity for cystatin C is 96.2% while the same for creatinine is 83.9% (Table 3).

Table 2

Laboratory data for participants stratified by GFR levels (n = 106)

	<15	**16-29**	**30-59**	**60-89**
Total Number	**20**	**36**	**38**	**12**
Age (years)	54.6 ± 14.14	50.83 ± 14.74	52.16 ± 14.14	38.33 ± 19.46
Weight (kg)	62.4 ± 16.49	66.2 ± 7.86	63.10 ± 15.2	62 ± 17.34
Height (cm)	163.8 ± 7.26	162.6 ± 9.50	162.3 ± 8.74	164.5 ± 12.40
iGFR(ml/min/1.73m^2)	10.99 ± 2.20	22.52 ± 4.48	38.94 ± 7.16	67.4 ± 7.87
S.Cystatin C (mg/l)	4.17 ± 0.75	3.90 ± 0.40	2.21 ± 0.61	2.04 ± 0.18
S.Creatinine (mg/dl)	5.3 ± 2.32	4.13 ± 1.6	2.47 ± 1.39	2.28 ± 0.25

GFR levels (ml/ min/1.73m^2)

Table 3
Area under the ROC curve for cystatin C and creatinine

Variables	area	std. error	lower bound*	upper bound*	Sensitivity (%)
Cystatin C (mg/l)	0.962	0.024	0.906	0.989	96.2
Creatinine (mg/dl)	0.841	0.035	0.878	0.897	83.9

**95 % Confidence Interval*

DISCUSSION

Kidney failure due to CKD is preceded by a stage of variable length during which GFR decreases. Despite all its disadvantages, serum creatinine concentration is still widely used for GFR estimation, as it is simple and cheap. Previous investigations have suggested that cystatin C might be a superior indicator of GFR compared with creatinine[9-11]. In the present study wherein 106 patients with CKD (stages 2–5), the correlation between ^{99m}Tc-DTPA renal scan and serum cystatin C was better than the correlation between ^{99m}Tc-DTPA renal scan and serum creatinine. The results of our study indicate that serum cystatin C is a reliable marker of GFR in patients with mild to end stage impairment of kidney function (stages 2– 5 of CKD; GFR <15 – >90 ml/min/1.73 m^2). All the patients in the study were analysed and according to our results, including the well-defined patients with CKD stages 2–5 (GFR <15 – >90 ml/min/1.73 m^2), serum cystatin C had a significantly higher diagnostic accuracy than serum creatinine. In this study, only 106 patients with different stages of CKD (GFR from 8 to 95 ml/min/1.73 m^2) were enrolled. Kyhse-Andersen *et al*.[6] included 27 healthy controls and 24 patients with reduced GFR (<80 ml/min/1.73 m^2) and found a significantly better correlation of serum cystatin C to GFR determined by clearance of iohexol than serum creatinine, and it revealed that the diagnostic accuracy of serum cystatin C for reduced GFR was superior to that of serum creatinine[6] and confirmed in this study also. Randers et al[15](2000) found that cystatin C was more sensitive than creatinine for mild decrease in GFR by ^{99m}Tc-DTPA clearance as evidenced by ROC analysis. Similar results are reported by this study too. Newman et al[7,13] , Hojs et al [18] & Soto K et al [19] concluded that in addition to being a better estimator of GFR than creatinine, cystatin C was a more sensitive marker than creatinine for small changes in GFR.

CONCLUSION

The results of the present study have confirmed that serum cystatin C is found to be a sensitive and better marker of impaired renal function when compared to serum creatinine. The cost of cystatin C is limiting factor in India, as its sustained use may make it more economical, if more patients are subjected to this test which is more accurate as reported in this study.

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