SERUM CYSTATIN C AS A SENSITIVE MARKER OF GFR IN ELDERLY PATIENTS WITH CHRONIC KIDNEY DISEASE

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Abstract

Chronic kidney disease (CKD) is a rapidly growing global health problem. Cystatin C has been proposed as an endogenous marker for the assessment of kidney function in CKD. The objective of the present study was to compare the serum cystatin C (Scys) and serum creatinine (Scr) in elderly patients with CKD. The glomerular flitration rate (GFR) of 92 patients was determined using 99m Tc- diethylene triamine penta-acetic acid (DTPA) clearance. Scr was determined by kinetic method using jaffe reaction. Scys was analysed by particle enhanced immuno turbidity (PETIA) method. Scys and Scr levels were significantly higher in the kidney failure group as compared with the advanced CKD group and advanced CKD group as compared with the moderate CKD ($p < 0.0001$). When compared with DTPA clearance, the Pearson's correlation coefficient for Scys was -0.779 ($p < 0.001$) while for Scr, it was -0.609 ($p < 0.001$). The ROC plots had an 'area under the curve' value of 0.992 for Scys and 0.970 for Scr. The present study demonstrated that determination of Scys might be useful in the assessment of renal function in elderly patients with CKD and is a potentially better marker than Scr.

Keywords: cystatin C, creatinine, DTPA clearance, chronic kidney failure.

I. INTRODUCTION

Chronic kidney disease (CKD) is a rapidly growing global health problem. Glomerular filtration rate (GFR) provides an excellent measure of the assessing renal function of the kidneys but it involves considerable effort, cost and time (1). The most commonly used measure of renal function (GFR) in clinical medicine is the serum creatinine (Scr). To use the Scr level as a marker of renal function, creatinine concentrations are influenced by factors such as age, gender muscle mass, tubular secretion, physical activity, and diet (2). GFR can be estimated by measuring creatinine clearance using Scr levels and a timed urine specimen. However, measuring creatinine clearance is time consuming and fraught with errors of timing and collection (3). In view of these difficulties, a number of mathematical formulae have been derived to determine GFR based on Scr such as Cockroft-Gault equation (CG) and Modification of Diet in Renal Disease (MDRD). These formulae include anthropometric variables such as body weight, gender, age and race to compensate for the inadequacies of creatinine level as a marker of GFR. However even including these many variables, the formulae have several limitations in estimating the GFR (4).

As elderly patients often have low muscle mass and poor nutrition, Scr may remain in the normal range despite decreasing GFR and therefore renal impairment may go unrecognised. Ageing is also associated with decreasing GFR, at a yearly rate of approximately 1 ml/min/1.73 m2 in those over the age of 40 years (5). Moreover, failure to appreciate renal insufficiency commonly results in drug dosage errors in older people (6). Thus, there is a crucial for suitable alternative endogenous markers of GFR in elderly.

Several investigations have been suggested that, the Scys is better marker of GFR than Scr (7). Cystatin C is a nonglycoylated, low molecular – mass (13kDa) basic protein that is a member of the cystatin superfamily of cysteine protease inhibitors. It consists of 120 amino acids and is produced by all nucleated cells and produced stable rate which is unaffected by inflammatory process, sex, age and diet (8). Cystatin C is freely filtered through the glomerular membrane and degraded by proximal tubular cells. The serum concentration of this protein shown to correlate with GFR of the individual and, in combination with this stable production rate, suggests that cystatin C may be potentially new marker of GFR (9).

The objective of the present study was to compare the Scys and the Scr in elderly patients with CKD and to determine the correlation of SCr, SCys and calculated GFR (MDRD and Orebro) with GFR determined using DTPA clearances.

II. MATERIALS AND METHODS

A total of 92 patients ranging in age from 60 to 82 years were included in this study. Ethica clearance for this study was obtained from the Ethical Committee of PSG Institute of Medical Sciences & Research. Patients undergoing dialysis were excluded while those with diabetes mellitus, systemic hypertension, autosomal dominant polycystic kidney diseases were included in the study. Patients were classified in to three group's namely moderate CKD, advanced CKD and kidney failure based on DTPA clearance (10).

Venous blood samples were collected into plain Becton Dickinson vacutainers with gel, from patients attending the nephrology OPD of the hospital. The blood sample was allowed to clot and the serum was used immediately for the estimation of, creatinine and cystatin C. GFR was determined by DTPA renal dynamic imaging using modified Gate's method. The technique is based on the fact that the fractional renal uptake of intravenously administered DTPA within 2 to3 minutes after radio tracer arrival within the kidneys is proportional to the GFR. After image acquisition, the GFR was automatically calculated by computer according to Gate's algorithm (11). Urea was determined using kinetic urease and glutamate dehydrogenase method (Olympus, Japan) (12), Creatinine was analysed by a rate blanked modified Jaffe's method (Olympus, Japan) (12). Both assays were implemented on an Olympus AU 400 clinical chemistry (Olympus opticals, Japan) analyzer according to the laboratory procedure. SCys was measured by using a particle enhanced turbidimetric immuno assay (Gentian AS, Moss, Norway) and it was implemented on an Olympus AU 640 clinical chemistry analyzer (Olympus opticals, Japan).

Formulae used for calculation of GFR

GFR (MDRD) = 186x (SCr) – 1.154 x (age) -0.203 x 0.742 (if patient is female) (13)

GFR (Orebro) = - 14 + 100/ cystatin C. (14)

III. STATISTICAL ANALYSIS & RESULTS

Statistical analysis was performed using Med-calc software. The comparison of biochemical parameters of the three groups was done using the student 't' test. The correlation between the Scr and Scys was calculated by Pearson's correlation coefficient. Diagnostic sensitivity and specificity were studied using ROC curves.

Table 1. shows, Scr as well Scys have been found to be significantly higher in the kidney failure group when compared with the advanced CKD group and advanced CKD group when compared with the moderate CKD with p values < 0.0001. Similarly the clearance of creatinine based on MDRD formula and the clearance of cystatin C based on Orebro formula are significantly higher in the kidney failure group when compared with the advanced CKD group and advanced CKD group when compared with the moderate CKD.

Table 1. Biochemical data of the studied subjects

	Moderate CKD	Advanced CKD	Kidney Failure
N	32	30	30
Age(yrs)	60.34±1.30	59.06±10.44*	52.46±14.19**
Creatinine(mgs/dL)	2.07±0.55	4.39±0.88*	9.40±3.30**
CystatinC(mg/L)	1.7±0.63	3.25±0.90*	4.90±1.23**
DTPA(mL/min/1.73m²)	48.4±23.27	24.33±8.79*	14.20±4.36**
MDRD(mL/min/1.73m²)	36.59±13.81	14 ± 3.69 *	6.96±2.31**
Orebro(mL/min/1.73m²)	50.54±32.69	19.05±8.91*	7.72±5.78**

Values are mean ± SD and ** indicates p Values<0.0001 moderate CKD Vs advanced CKD & advanced CKD Vs kidney failure for all parameters.

Table 2. Correlation between Scr and Scys & MDRD and Orebro with GFR (DTPA)

	Total	p value
GFRVsCreatinine	0.609	<0.001
GFRVsCystatinC	0.779	<0.001
GFRVsMDRD	0.744	<0.001
GFRVsOrebro	0.972	<0.001

Table 2. shows, both SCr and SCys showed a significant negative correlation with DTPA clearance. However the Pearson's correlation coefficient (r value) for SCys was -0.779 while for SCr, it was -0.609. The correlation coefficient (r value) between calculated GFR based on MDRD method and DTPA clearance was 0.744 while the calculated GFR based on Orebro formulae was 0.972. Although all these parameters correlated with DTPA clearance at a significance level <0.001, the Orebro formula showed the highest correlation.

ROC Analysis

The performance characteristics of Scr and Scys was analyzed using ROC curves in order to ascertain their sensitivity and specificity, The area under the curve for Scys was found to be 0.992 while for Scr, it was 0.0.970. The cut off was taken as DTPA clearance of 60ml/min/1.73m2 (Table 3).

Table 3. Sensitivity, specificity and accuracy of Scys and Scr in studied subjects

	AUC	SE	Sensitivity	Specificity	p Value
Scr	0.970	0.017	95	75	0.0001
Scys	0.992	0.0048	98	100	0.0001

IV. DISCUSSION

The results of our study indicate that Scys is a reliable and sensitive parameter to assess renal function in elderly patients with CKD. All the statistical tools used to analyze the results serve to underscore the fact that this parameter is certainly useful not only to diagnose renal disease but to also assess its progression.

Both parameters Scr as well Scys show significantly higher values in the kidney failure group over the advanced CKD group and advanced CKD group over the moderate CKD group. The results have therefore shown that Scys can be used to segregate patients into moderate CKD, advanced CKD and kidney failure as efficiently as Scr.

The Pearson's correlation coefficient evaluates the usefulness of Scys over the whole spectrum of renal dysfunction in order to assess whether this analyte shows a parallel rise as the disease progresses and the GFR falls. Scys showed a higher negative correlation than Scr with DTPA clearance which is considered as the gold standard. The cystatin C based Orebro formula also showed a better correlation with DTPA clearance than creatinine based MDRD formula.

Studies by Filser et al (15) and O'Riordan et al (6) reported that cystatin C is superior to serum creatinine for the detection of mild renal impairment in elderly population. This is similar to findings of Elise et al (16), who noted serum cystatin C is a more reliable marker of glomerular function compared with serum creatinine in the elderly and offers a simple screening assay for the detection of early renal impairment in the ageing kidney.

ROC analysis is now a standard tool to assess, define, and compare the diagnostic validity of tests. In the present study, the ROC curves of Scr and Scys showed a high degree of sensitivity and specificity when compared with GFR estimation using DTPA at the cut off value 60 ml/min/1.73m2. There was no significant difference between Scys and Scr for detecting GFR less than 80ml/min/1.73m2 as determined by DTPA clearance. The similar study was reported by Randers et al (17). The results showed the superiority of the Orebro formula over the MDRD formula in predicting creatinine clearance in elderly patients with CKD.

Shlipauk et al (18) have reported that Scys is a stronger predictor of the risk of death and cardiovascular events in elderly persons than is creatinine. The estimation of Scys is therefore useful in not only following the progress of CKD but also in assessing the risk of developing cardiovascular complications in these patients.

Our present study demonstrated that determination of Scys might be useful in the detection of renal dysfunction in elderly patients with CKD. Scys shows promise as a valuable potential marker than Scr to describe pathophysiologic, diagnostic, prognostic and therapeutic implication of GFR loss among elderly patients with CKD.

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