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Research Article

A COMPARISON BETWEEN SERUM CREATININE AND CYSTATIN C-BASED FORMULAE: ESTIMATING GLOMERULAR FILTRATION RATE IN CHRONIC KIDNEY DISEASE PATIENTS

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ABSTRACT

Background-Progression of CKD is determined by fall in GFR. Currently GFR estimation is done with S.Creatinine based formulae. S.Creatinine estimation is dependent upon various factors and hence not an accurate marker of renal function. Recently S.Cystatin C estimation is found to be comparable with S.Creatinine estimation as a marker of renal function. Many studies have not been done to calculate GFR using S.Cystatin C based formulae to compare its accuracy with S.Creatinine based formulae. Hence the current study is done with this objective in mind.
Materials and Methods- GFR was estimated using two equations (LeBricon and Hoek) that are based on serum cystatin C and two equations (Cockcroft-Gault and MDRD) that are based on serum creatinine in 182 CKD patients. GFR measured by using radiolabelled diethylenetriaminepentaaceticacid (^{99m}Tc-DTPA) renal scan method is used as the standard for comparison.
Results-The Average isotope GFR was 33.81 (ranged from 6 - 110 ml/min/1.73m^2).Correlation coefficients of all calculated GFR, were compared with measured GFR. The cystatin C based equations correlated well with all stages of the CKD than creatinine based equations.
Conclusion-Cystatin C based formulae provides a better diagnostic performance than creatinine based equations for GFR calculation in CKD population. The LeBricon formula is most accurate.

Key Words: Cystatin C, Glomerular filtration rate, MDRD, Hoek, LeBricon.

INTRODUCTION

Chronic kidney disease is a major public health problem with increasing incidence and prevalence associated with poor out come and high cost [1,2]. Determination of glomerular filtration rate (GFR) with high accuracy requires the use of invasive techniques based on measuring the plasma clearance rate of injected substances that are exclusively excreted via glomerular filtration, e.g.; inulin, ^{51}Cr-EDTA, ^{99m}Tc-diethylenetripentaaceticacid or radiographic contrast media such as ^{125}I-Iothalamate and iohexol. These procedures are labor intensive and not entirely free of risk for the patient. The plasma or serum concentrations of endogenous substances, particularly creatinine have therefore been used as markers for GFR for more than a century. However, it has become evident that the creatinine concentration is far from ideal as a GFR marker because it is significantly influenced not only by GFR but also by factors such as muscle mass, diet, gender, age and tubular secretion [3-7]. To compensate for the inadequacies of the creatinine concentration as a GFR marker, there had been several successful attempts at constructing GFR prediction equations including additional parameters.

Plasma or serum cystatin C has been proposed as a marker for GFR [8–11], and several commercially available automated procedures for rapid determination of cystatin C have been reported[12–15]. In the present study, we have attempted to compare the diagnostic performance of cystatin C based prediction equations and creatinine based prediction equations with isotope GFR.

MATERIALS AND METHODS

Study Population

One hundred and eighty two CKD patients (136 males, 46 females) with mean age of 51.7 years (range, 20 to 85 years) were included for the present study. Written informed consent was obtained from the patients.

GFR Measurement using ^{99m}Tc-DTPA Renography

The patients are made to lie down on a bed in the supine position. ^{99m}Tc-DTPA was injected through an indwelling butterfly needle in to anticubital vein and followed by infusion of 20 ml of normal saline. Frames of 128 x 128 matrix were recorded with an online- computer, initially at one second for one minute and then at 10 seconds for 20 minutes.

Region of interest (ROI) over each kidney assigned manually on the frame was added from 1 to 3 minutes following injection . The semi lunar background ROI around each kidney was defined and was modified for the inferior ROI's in the original gates. The background corrected time-activity curve was generated and the renal update of individual kidney for one minute period from 2 to 3 minutes after the injection was calculated. The GFR was automatically estimated by a commercially available computer programme (E. CAM, Siemens, USA) according to the Gate's[16] algorithm.

Creatinine and Cystatin C assay

All creatinine measurements were performed in the same laboratory. Blood samples were obtained simultaneously with the GFR measurement. Serum creatinine was measured by Jaffe's method using semi auto analyzer (Merck 300, USA).Serum cystatin C was measured by particle enhanced nephelometric immuno assay (PENIA) (Dade Behring, Germany).

Creatinine Based Estimation of GFR

The two formulae studied to predict GFR from serum creatinine were the one proposed by Cockcroft and Gault (13).

$$GFR_{CG} = [(140\text{-age}) \times \text{weight (kg)}] / 72 \times \text{S.Cr (mg/dl)}$$

(for women, multiply with 0.8) and the one simplified from the MDRD formula (14).

$$GFR_{MDRD} = 186 \times (\text{S.Cr in mg/dl})^{-1.54} \times \text{age}^{-0.203}$$

(for women, multiply with 0.742)

Where S.cr is serum creatinine concentration.

A correction for body surface area (BSA) was necessary for the CG formula. This was performed using estimated BSA according to Haycock's equation (15).

Cystatin C based estimation of GFR

GFR estimated using two equations that were based on serum cystatin C one proposed by Hoek (17):

$$GFR_{Hoek} = -4.32 + (80.35 \times 1/\text{ cystatin C})$$

and the another proposed by Lebricon (18):

$$GFR_{LeBricon} = [(78) \times (1/\text{cystatin C})] + 4$$

GFR was measured using ^{99m}Tc-DTPA and all formulae were compared with it. In this study isotope GFR was considered gold

standard and all calculated formulae were compared with it, in the absence of inulin clearance.

Statistical analysis

Correlation coefficients and stepwise regression analysis were carried out using medcalc 8.1 statistical software (Belgium). A *P* Value <0.05 was considered statistically significant.

RESULTS

A total of one hundred and eighty two patients (136 men and 46 women) were divided into four stages based on iGFR levels as follows (Table 1):

I) GFR < 15 ml / min / 1.73 m^2 (10.17± 2.4; N= 32),

II) GFR 16-29 ml / min / 1.73 m^2 (22.58 ±4.4; N=58),

III) GFR 30- 59 ml / min / 1.73 m^2 (39.05 ± 7; N=70), and

IV) GFR 60-89 ml /min / 1.73m^2 (69.62±8; N=22).

In the stage I, the measured GFR was compared with creatinine based formulae and cystatin C based formulae. Among these formulae, cystatin C based formulae Hoek (*P*=0.0024) and LeBricon (*P*=<0.0001) show significant correlation than the creatinine based formulae CG (*P*=0.013) and MDRD (*P*=0.058), particularly the LeBricon shows higher correlation coefficient than the others. Similarly, in the II stage also the cystatin C based formulae Hoek (*P*=<0.0001) and LeBricon (*P*=<0.0001) show the significant correlation than creatinine based formulae CG (*P*=0.0812) and MDRD (*P*=0.002). In the III and IV stages of CKD, the cystatin C based formulae correlated well with iGFR. The creatinine based formulae did not show significant correlation with iGFR in the above stages. Between the cystatin C based formulae LeBricon shows the higher correlation coefficients than Hoek in all stages of CKD (Table 2).

Table1: Patients characteristics

	Mean ±SD	Median (Range)
Age (Years)	51.76±14.06	54(20-85)
Body mass index (Kg/m^2)	22.67±4.45	22.9(14.5-30.8)
Body surface area (m^2)	1.68±0.18	1.67(1.13-2.07)
Serum Creatinine (mg/dl)	3.60±2.20	3.0 (0.8-10)
Serum cystatin C (mg/l)	3.01±1.29	2.99 (0.86-8)
iGFR (ml/min/1.73m^2)	33.8±21.42	29.7 (6-110)
Sex (n [%])		
Male	(136 [74.7%])	
Female	(46 [25.3%	
CKD Stages	**(n [**	
GFR<15 ml/min/1.73m^2	32 [17.5%]	
GFR 16-29 ml/min/1.73m^2	58 [31.8%]	
GFR 30-59 ml/min/1.73m^2	70 [38.4%]	
GFR 60-89 ml/min/1.73m^2	22 [1	

Table 2: **Comparative representation of Measured GFR (iGFR) vs Estimated GFRs using various formulae**

GFR Levels ml/min/1.73m^2	N	iGFR		S.Cr			*S.Cys C*		
					Estimated			Estimated	
				Measured S.Cr	CG	MDRD	Measured S.Cys C	Lebricon	Hoek
< 15	32	Mean ± SD	10.17±2.4	6.2±2.55	13.29±7.65	12.6±8.48	4.86±0.93	10.45±2.35	12.6±2.42
		r		-0.395	0.433	0.388	-0.516	0.918	0.518
		P		0.025	0.0132	0.058	0.0025	<0.0001	0.0024
16-29	58	Mean ± SD	22.58±4.4	3.92±1.59	24.76±12.7	20.72±12.73	3.6±0.28	23.96±3.22	18.41±2.37
		r		-0.239	0.2309	0.397	-0.549	0.794	0.671
		P		0.025	0.0812	0.002	<0.0001	<0.0001	<0.0001
30-59	70	Mean ± SD	39.05±7	2.99±1.54	30.22±17.93	28.34±16.36	2.31±0.46	40.38±11.09	33.15±11.43
		r		-0.137	0.337	0.215	-0.724	0.5546	0.5545
		P		0.258	0.0482	0.079	<0.0001	<0.0001	<0.0001
60-89	22	Mean ± SD	69.62±8	1.34±0.28	62.21±24.64	61.46±23.29	1.16±0.16	72.57±10.57	66.31±10.88
		r		0.0237	-0.0231	-0.169	-0.793	0.827	0.729
		P		0.9168	0.2414	0.4524	<0.0001	<0.0001	0.007

S.Cr- Serum creatinine; S.Cys C – Serum Cystatin C

DISCUSSION

Among the different methods for cystatin C-based GFR stimulations, the equations proposed by Filler and Lepage[19] and Le Bricon and colleagues[18]provided a more accurate estimate of GFR than creatinine or other cystatin C-based equations in kidney transplant recipients[22, 25]

According to the previous reports on the accuracy of cystatin C levels for measurements of GFR, we planned a study to compare the performance of the two creatinine-based equations with two cystatin C-based equations in chronic kidney disease patients. In our study, significant differences were shown between creatinine-based and cystatin C-based equations. Creatinine levels vary due to muscle mass and the tubular secretion of creatinine which makes the test prone to some limitations. Cystatin C is produced endogenously at a constant rate, freely filtered in the glomeruli, and completely reabsorbed and catabolized by the renal tubule cells, but it is not affected by severe illness, age, gender, height, and obesity; therefore, it is found to be a reliable indicator of kidney function. This could be the cause of the difference between the equations which was confirmed by other studies, too[23, 24]. This study demonstrates that the cystatin C based prediction equation of LeBricon and Hoek are more accurate at estimating GFR than the conventional creatinine based equations. The cystatin C based prediction equations were derived in a variety of population, including both adult and pediatric age group as well as transplant and non-transplant patients [18-21]. Christine W et al [21] published that Filler and LeBricon equations in renal transplant recipients were more accurate in predicting GFR than creatinine based equations. In the present study, we have observed that both LeBricon and Hoek equations for estimating GFR are better than MDRD and CG formulae in chronic kidney disease.

CONCLUSION

In conclusion, this analysis has shown that

1) GFR can be estimated in chronic kidney disease patients using the cystatin C based prediction equations of LeBricon and Hoek and the LeBricon formula is better of the two.

2) Cystatin C based estimates of GFR are more reliable than the traditional creatinine based estimates.

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