

Cystatin C levels in healthy kidney donors and its correlation with GFR by creatinine clearance

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Abstract

Objective: To determine Serum Cystatin C (S.CysC) levels in healthy potential kidney donors and its correlation with Serum Creatinine (S.Cr), Glomerular filtration rate (GFR) by 24 hour urinary Creatinine clearance (CCL) and GFR by formulae of Cockcroft Gault (CCG) and Modification of diet in Renal Disease (MDRD).

Methods: A Cross sectional study was conducted at Sindh Institute of Urology and Transplantation (SIUT), Karachi, between June and December 2012. One hundred and three potential healthy kidney donors were enrolled in the study to measure their S.CysC and correlate it with S.Cr, CCL and GFR by CCG and MDRD. Statistical analysis was done by SPSS 17.

Results: The mean age of the healthy kidney donors was 32.19±8.27 years with a M:F ratio of 1.86:1. The mean Serum Creatinine (S.Cr) was 0.86±0.18 mg/dl and mean S.CysC was 0.88±0.12 mg/dl. S.CysC showed significant correlation with S.Cr ($r = 0.78, p < 0.001$), CCL ($r = 0.67, p < 0.001$), GFR CCG ($r = 0.54, p < 0.001$) and GFR MDRD ($r = 0.67, p < 0.001$). Correlation of S.CysC was better than S.Cr for CCL, S.Cr (0.60) vs S.CysC (0.67) and GFR CCG, S.Cr (0.41) vs S.CysC (0.54). Correlation was comparable for MDRD, S.Cr (0.67) vs S.CysC (0.67).

Conclusion: S.CysC is better marker of kidney function in potential healthy kidney donors. It is a reliable, convenient and economical marker that can be used especially in routine clinical practice.

Keywords: Cystatin C, Kidney donor, Glomerular Filtration rate. (JPMA 64: 286; 2014)

Introduction

Renal transplantation is the therapy of choice for end-stage renal disease (ESRD) as it offers improved quality of life and better patient survival as compared to dialysis.¹ In the absence of deceased donor programmes in developing countries, living donors are the principle source of kidneys for transplantation. It, therefore, becomes essential that kidney donors are attentively screened for renal function, so as to ensure good long term renal function of both recipients and donors.²

Renal function is evaluated by measuring Glomerular filtration rate (GFR) by exogenous as well as endogenous markers as it provides an excellent measure of the functioning capacity of the kidney.³ Exogenous markers include inulin and radioisotopes ^{99m}Tc-mercuric, ⁵¹Cr-EDTA and ¹²⁵I-iothalamate³ and endogenous markers include serum creatinine (S.Cr) and serum cystatin C (S.CysC).⁴ Although, Inulin clearance is a good method of measuring GFR, its clinical usefulness is limited due to the continuous infusion of the drug during evaluation.⁵ Radioisotopes on the other hand are invasive, nephrotoxic and costly and hence can not be routinely

employed in the work up of potential kidney donor.⁶ GFR based on creatinine clearance (CCL) in a 24 hour urine collection is the most widely used method to assess renal function. However this method has drawbacks as its value can be affected by body muscle mass, size and sex of the individual and variation in production rate and tubular secretion of creatinine.³ Furthermore, urine collection for 24-hour can be affected by patient compliance and improper collection of specimen results in under or overestimation of GFR.⁷ In recent years, S.CysC has been shown to be a better marker of GFR than S.Cr in a large cohort of diverse population.⁸ S.CysC levels have been shown to detect subtle changes in GFR in healthy individuals.⁹ It has also been shown to be a better marker of GFR than S.Cr in the elderly and in patients with chronic renal failure⁴ and in cancer patients.¹⁰ S.CysC is a 133 kilo Dalton (KD) protein, produced by all human nucleated cells. It passes freely through the glomerular membrane, is completely reabsorbed and catabolized in the tubules.¹¹ Therefore, S.CysC levels in blood primarily depend on the GFR of the individual and thus it provides a tool to assess renal function by a simple blood test.

This study was undertaken to determine S.CysC levels in healthy potential kidney donors and to assess its correlation with markers of GFR including CCL, creatinine based GFR formulae: Cockcroft Gault (CCG)¹² and GFR by Modification of Diet in Renal Disease (MDRD).¹³

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Materials and Methods

This is a single-center cross sectional study involving 103 potential healthy kidney donors. Initial clinical and biochemical evaluation was based on guidelines of the Amsterdam forum.¹⁴ Informed consent was obtained from all participants for kidney donation and the study was approved by the Ethical Review Committee (ERC) of the Institute. Each potential donor underwent a series of biochemical evaluations including S.CysC, S.Cr and 24 hour urine for CCL. All samples were analyzed according to hospital routines.

S.CysC was measured by particle-based immunoturbidimetric assay (RANDOX) on VITA LAB Selectra E auto analyzer (Merck). Creatinine was measured by Jaffe's alkaline picrate method using Beckmen Coulter Cx3 auto analyzer. The methodology, auto analyzer and reference values for S.CysC, Cr remained same during entire period of study. The equipment was calibrated daily and a quality control check was carried out 3 times a day.

The 24 hour urine Creatinine clearance (ml/min/1.73m²) was assessed by formula: = [Volume (ml / minute) x Urinary Creatinine (mg/dl) x 1.73] ÷ [Serum creatinine (mg/dl) x Body surface area].

GFR was calculated by Cockcroft-Gault formula (CCG) based on creatinine as follows;

CCG (ml/min/1.73m²) = [(140-age) x weight] ÷ [72 x S.Cr] x (0.85 if female)

GFR was calculated by MDRD based on creatinine as follows;

MDRD (ml/min/1.73m²) = 186 x S.Cr^{-1.154} x age^[-0.203] x (0.742 if female)

Reference range in the study for S.CysC was 0.57-1.05 mg/L and GFR by CCL as 80-140 ml/min/1.73m².

For statistical analysis, the data were analyzed by using the statistical package for social science SPSS (Release 17.0, standard version, copy right © SPSS; 1089-02). Mean ± Standard deviation were expressed for quantitative variables (age, S.CysC, S.Cr, CCL, GFR CCG, GFR MDRD). Frequency in % was obtained for qualitative variable. A p-value <0.05 was considered as significant. Correlation between variables was studied using Pearson correlation coefficient.

Results

The baseline characteristics of 103 healthy kidney donors are shown in Table-1. The mean age was 32.19±8.27 years, with a M:F ratio of 1.86:1. The mean S.Cr was 0.86±0.18mg/dl and S.CysC 0.88±0.12mg/L. Mean S.Cr and S.CysC were significantly higher in males as compared to females. The mean CCL was 99.08±22.25 ml/min/1.73m², GFR by CCG was 99.93±24.98 ml/min/1.73m² and MDRD was 103.14±22.09 ml/min/1.73m².

S.CysC showed significant correlation with S.Cr (r= 0.78, p<0.001), CCL (r= 0.67, p<0.001); GFR calculated by CCG

Table-1: Baseline parameters in potential healthy kidney donors.

Parameters	All Donors (n=103)	Male Donors (n=67) 65%	Female Donors (n=36) 35%	p value Male vs Female
Age (Year)				
Mean	32.19+8.27	30.88+7.71	34.64+8.81	0.027
Range	(19 – 50)	(19 – 50)	(22 – 50)	
S. Cr (mg/dl)				
Mean	0.86+0.18	0.93+0.16	0.73+0.12	0.001
Range	(0.51 – 1.28)	(0.57 – 1.28)	(0.51 – 0.98)	
S.CysC (mg/L)				
Mean	0.88+0.12	0.91+0.11	0.81+0.12	0.001
Range	(0.49 – 1.18)	(0.49 – 1.18)	(0.55 – 1.09)	
CCL (ml/min/1.73m²)				
Mean	99.08+22.25	98.70+21.23	99.79+24.35	0.814
Range	(61 – 166)	(61– 166)	(63 – 166)	
GFR-CCG (ml/min/1.73m²)				
Mean	99.93+24.98	104.07+25.34	92.23+22.66	0.21
Range	(62 – 161)	(64 – 161)	(62 – 150)	
GFR-MDRD (ml/min/1.73m²)				
Mean	103.14+22.09	104.77+23.12	100.10+19.99	0.309
Range	(65 – 166)	(66 – 166)	(67 – 144)	

S.Cr: Serum Creatinine. S. CysC: Serum Cystatin C. CCL: Creatinine Clearance. GFR-CCG: Glomerular Filtration Rate-Cockcroft-Gault. GFR-MDRD: Glomerular Filtration Rate-Modification of Diet in Renal Disease.

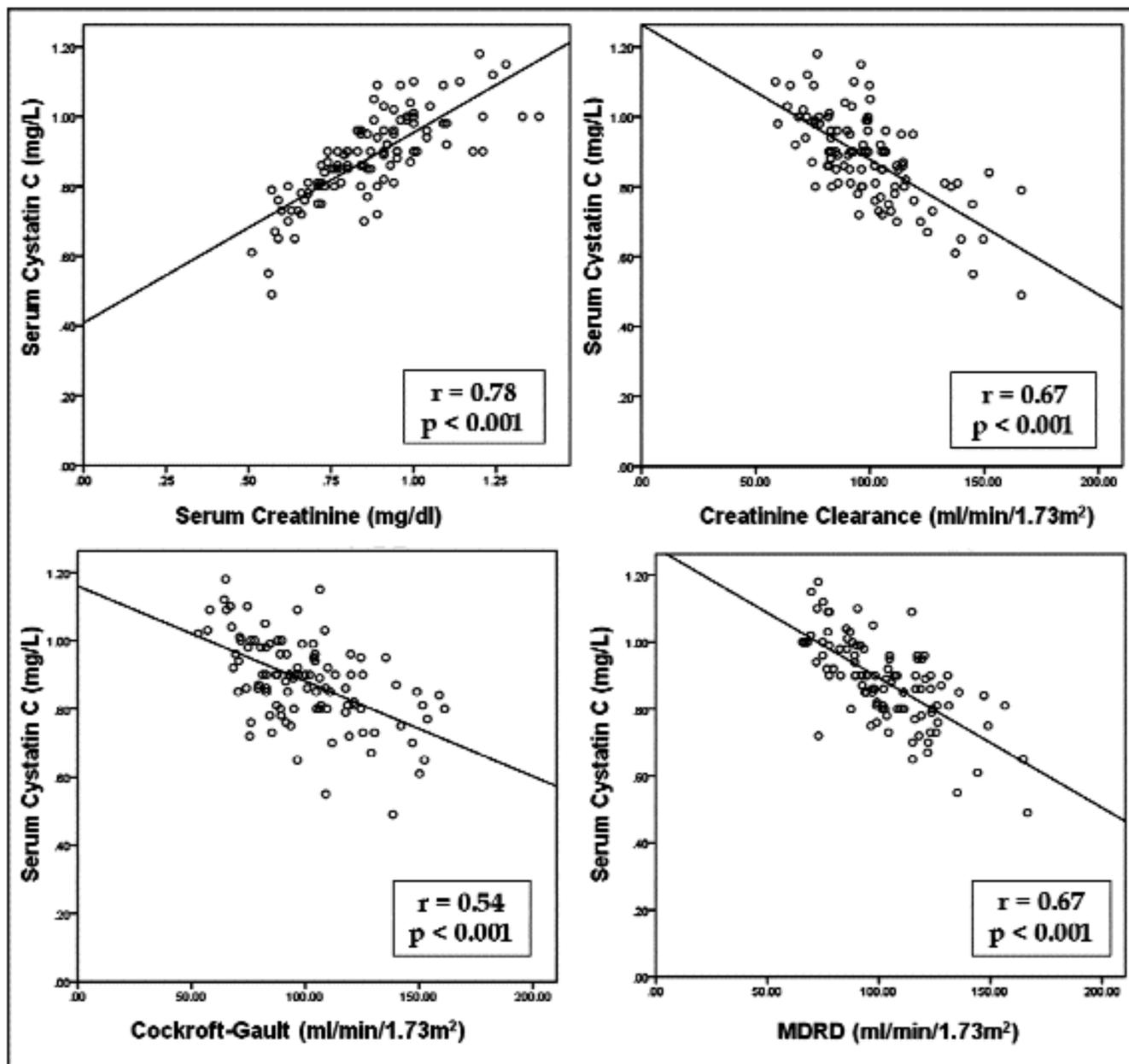


Figure: Correlation of S.CysC with S.Cr, CCL, CCG and MDRD.

Table-2: An equivalence guideline of S.CysC with GFR by CCL.

Cystatin C (mg/L)	GFR (CCL) ml/min/1.73m ²
0.5 - 0.6	135 - 145
0.6 - 0.7	125 - 135
0.7 - 0.8	110 - 125
0.8 - 0.9	100 - 110
0.9 - 1.0	88 - 100
1.0 - 1.1	75 - 88
1.1 - 1.2	65 - 75

($r = 0.54$, $p < 0.001$) and MDRD ($r = 0.67$, $p < 0.001$) (Figure). When distribution of S.CysC was stratified by sex, correlation of S.CysC with S.Cr for females was ($r = 0.86$, $p < 0.001$) and males ($r = 0.70$, $p < 0.001$), CCL for females was ($r = 0.78$, $p < 0.001$) and males ($r = 0.68$, $p < 0.001$). Correlation of S.CysC with GFR CCG for females was ($r = 0.70$, $p < 0.001$) and males ($r = 0.69$, $p < 0.001$) and correlation with GFR MDRD for females was ($r = 0.82$, $p < 0.001$) and males ($r = 0.74$, $p < 0.001$).

S.CysC showed better correlation with CCL and CCG as

compared to S.Cr. The correlation of S.Cr with CCL was ($r=0.60$, $p<0.001$) and with CCG was ($r=0.41$, $p<0.001$) as compared to S.Cys with CCL ($r=0.67$, $p<0.001$) and with CCG was ($r=0.54$, $p<0.001$). The correlation of S.Cr and S.CysC was similar for MDRD with ($r=0.67$, $p<0.001$ and $r=0.67$, $p<0.001$ respectively). A guideline of equivalence of S.CysC mg/L blood levels with GFR by CCL ml/min/1.73m² is given in Table-2.

Discussion

Accuracy in the estimation of GFR is essential for interpretation of symptoms, signs and laboratory parameters that may indicate kidney disease. This is specially important for selecting kidney donors for live related renal transplantation. The long term function and survival of the transplanted kidney and the remaining kidney in the donor depends on the functional renal capacity of the donor i.e. GFR.¹⁵ S.CysC has been found to be a better marker of GFR in healthy individual, kidney donors and patients with Chronic Kidney Disease.^{4,8} The level of S.CysC in our study population was found to be 0.88 ± 0.12 mg/L. An earlier report from Lahore in the north of Pakistan reported a higher mean S.CysC of 1.39 ± 0.10 in males and 1.19 ± 0.10 in females as compared to 0.91 mg/L and 0.81 mg/L represented in our study.¹⁶ The difference may be due to younger population in our study due to preference for younger donors with an age range of 19-50 years as compared to 18-60 in the Lahore study.¹⁶ However, our results are comparable to that reported from India of 0.71 ± 0.12 mg/L⁹ and Canada 0.79 ± 0.13 mg/L.¹⁷ A significant sex difference was observed in S.CysC levels with higher levels in males as compared to females. This was also observed by others where levels were higher in males.^{9,18} However in another study of 300 healthy subjects S.CysC levels were higher in females 0.77 ± 0.11 mg/L as compared to males 0.72 ± 0.09 mg/L.¹⁹ These contrasting reports suggest further evaluation of the impact of age and sex on S.CysC levels as it has been reported that levels are affected by gender and age.²⁰

S.CysC showed significant correlation with CCL, CCG and MRDR which have been reported by other studies. Correlations for CCL ($r=0.76$, $p<0.001$)⁹ and ($r=0.54$, $p<0.001$),¹⁷ for CCG ($r=0.50$, $p<0.002$)⁹ and ($r=0.33$, $p<0.01$)¹⁷ and for MDRD ($r=0.59$, $p<0.001$)⁹ and ($r=0.59$, $p<0.01$).¹⁷ The GFR assessed by CCL in our population was 99.08 ± 22.25 ml/min/1.73m². This is lower than reported in western studies of 120 ± 27 ml/min/1.73m²¹⁷ and comparable to that reported from India 98.70 ± 8.87 ml/min/1.73m².²⁹ This may be a reflection of difference in muscle mass between South Asian and European population. CCL reported from China has a

mean of 129.5 ± 23.9 ml/min/1.73m².²¹ An earlier study from Pakistan showed significantly higher values of S.CysC in over weight as compared to healthy subjects which may be reflected in GFR values.¹⁶

The objective of this study was to identify the usefulness of S.CysC as a marker of GFR in potential donors. This study has shown that accurate estimate of GFR can be achieved by S.CysC as it significantly correlates with established markers of GFR, CCL, CCG and MDRD. These significant correlations have helped in developing a guideline for S.CysC level and GFR in our population. S.CysC is a simple blood test which avoids cumbersome collection of 24 hour urine for CCL estimation. This test has potential for determining the GFR of kidney donors and transplant recipients in follow-up clinics. Earlier studies in our population have evaluated S.CysC in healthy subjects and cancer patients.^{9,10} Further studies are required in our population with a large cohort to establish S.CysC as a routine test for estimation of GFR.

Acknowledgement

We are grateful to Mr. Hobin Daniel for typing of manuscript.

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