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ORIGINAL ARTICLE

Comparison of Estimated Glomerular Filtration Rate Using Different Analytes in Chronic Kidney Disease Patients

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ABSTRACT

BACKGROUND: Chronic kidney disease is a worldwide public health problem and one of the most common leading causes of morbidity and mortality. CKD is defined as kidney damage or glomerular filtration rate (GFR) <60 ml/min/1.73m^2 for 3 months or more, irrespective of cause. Glomerular filtration rate measurement is required for management of CKD patient by staging according to National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI). The aim of present study was to comparison of cystatin C and creatinine to measure glomerular filtration rate in chronic kidney disease patients. **MATERIALS AND METHODS**: A prospective study includes previously diagnosed 150 patients of chronic kidney disease (group I), 100 normal healthy subjects (group II) and subgroup III (≤40 years) and subgroup IV (≥41 years) were included. The blood samples were taken from each patient and analyzed for Cystatin C, creatinine and glomerular filtration rate was measured. Cystatin C level estimation was done by latex immuno-turbidimetric method and creatinine by Jaffe's kinetic method on fully auto analyser I-Lab 650 (Instrumentation laboratory USA) in Clinical Biochemistry Section, Laboratory Services Sir Takhtsinhji Hospital, Bhavnagar. Statistical significant correlation between creatinine and Cystatin c was done by Pearson correlation coefficient. **RESULTS:** Serum Cystatin C levels was significantly higher in study group in comparison to control group (4.66 ± 0.76 Vs 0.69± 0.12, p<0.0001). The estimated GFR by Cystatin c equation was also significantly lower in study group in comparison to control group (9.19 ± 2.42 Vs 142.49 ± 39.15, p< 0.0001). Serum creatinine levels were significantly higher in study group in comparison to control group (5.19 ± 0.86 Vs 0.69 ± 0.12, p<0.0001). The estimated GFR by creatinine (CG) formula were also significantly lower in study group in comparison to control group (18.07 ± 4.344 Vs 107.10 ± 26.20, p< 0.0001). **CONCLUSION**: On the basis of present study, it is concluded that Cystatin C seems to be a promising alternative endogenous marker to creatinine for estimation of glomerular filtration rate in chronic kidney disease patients. Serum cystatin C is directly related with glomerular filtration rate but not influenced with age, sex, diet and body weight as compare to serum creatinine.

Keywords: Cystatin C (CysC), Creatinine (SCr), Glomerular Filtration Rate (GFR), Chronic Kidney Disease (CKD), Cockcroft-Gault (CG) Formula.

INTRODUCTION

Chronic kidney disease (CKD) is a worldwide public health problem, both for the number of patients and cost of treatment involved. Globally, CKD is the 12th cause of death and the 17th cause of disability, respectively.[2] The approximate prevalence of chronic kidney disease is 800 per million populations in India. With increasing prevalence of CKD, attention is also required for cardio vascular disease (CVD), End stage renal disease (ESRD) and the consequent financial burden of renal replacement therapy (RRT) therefore importance of CKD and its risk factors has to be realized.[2]

CKD is defined as kidney damage or glomerular filtration rate (GFR) <60ml/min/1.73m^2 for 3 months or more, irrespective of cause.[3] The general mechanisms of renal progression advance sequentially through six stages that include hyperfiltration, proteinuria, cytokine bath, mononuclear cell infiltration, epithelial-mesenchymal transition, and fibrosis.[6] Kidney disease severity is classified in to five stages according to the level of GFR.[3] Glomerular filtration rate (GFR) is the best overall index of renal function in health and disease.[4]

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The gold-standard method for the determination of GFR is inulin clearance. However, inulin clearance is generally only used for scientific research because the method is cumbersome.[1]In day to day clinical practice an estimation of glomerular filtration rate (eGFR) is required for various reasons, like a) Assessment of renal function, b) Severity of renal disease, c) Calculation of proper drug dosage and d) Appraisal of renal involvement in systemic diseases.[16]

For calculating the glomerular filtration rate, the creatinine clearance formulas have been used but Creatinine clearance overestimates GFR because of tubular secretion. In normal renal function this accounts for 10-40% of GFR with marked interindividual variability. Tubular secretion can increase to more than 100% in patients with reduced renal function especially in glomerulopathic and proteinuric patients. For this reason, alternate molecules have been researched and studied about these molecules have been carried out. One of these agents is Cystatin C and it has 122-amino acid, 13-kd cysteine protease inhibitor which is produced by all nucleated cells and is independent of muscle mass and sex. Its production, unlike ß2- microglobulin is not affected by inflammatory states or malignancies. Cystatin C is eliminated by glomerular filtration and it is not secreted, but is reabsorbed by tubular epithelial cells and subsequently catabolized so that it does not return to the blood flow. Its measurement has been proposed as an alternative and more sensitive marker of glomerular filtration rate than creatinine particularly in patients with slight to moderately decreased glomerular filtration rate. We examined the relationship between Cystatin C and creatinine in this study.[16]

The present study is designed to estimate and compare glomerular filtration rate by serum Cystatin C and serum creatinine in patients of chronic kidney disease to see usefulness of serum Cystatin C over serum creatinine in routine clinical practice.

MATERIAL AND METHODS

A prospective study includes previously diagnosed 150 patients of chronic kidney disease (group I), 100 normal healthy subjects (group II) and subgroup III (≤40 years) and subgroup IV (≥41 years) were included. They were primarily diagnosed by clinical examination and Ultrasonographical findings show loss of Cortico Medullary Differentiation (CMD) and increased ecogenicity and further evaluated by biochemical investigations. All cases were admitted to the Medicine ward & dialysis was carried out in dialysis unit at Sir T. General Hospital, Bhavnagar (Gujarat). The subjects in control group were selected from the staff working in Sir T. General Hospital and people coming for their physical fitness to the hospital. The subjects in both groups were selected by using exclusion and inclusion criteria. The study was reviewed and approved by Human Ethics committee of Government Medical College, Bhavnagar (Gujarat) and there was no conflict of interest.

Written consent of patients was taken and they were instructed for sample collection. Blood samples were collected, centrifuged and the Cystatin C level estimation was done by latex immuno-turbidimetric method and creatinine by Jaffe's kinetic method on fully auto analyser I-Lab 650 (Instrumentation laboratory USA) in NABL accredited Clinical Biochemistry Laboratory, Laboratory Services Sir Takhtsinhji Hospital (LSSTH), Bhavnagar. Statistical analysis of result data were performed using Graph Pad Instat (version 3.00, Graph Pad Software, California USA). Data are presented as mean ± SD. Statistical correlation between Cystatin C and creatinine assessed by applying Pearson correlation coefficient test. A value $p<0.005$ was considered statistically significant.

For calculation of GFR from Cystatin C values measured with Quantita Cystatin C assay the following prediction equation is recommended using mg/L as the unit factor.

RESULTS

In the present study, 150 patients of chronic kidney disease were included with the mean age (45.96 ±10.00) years and out of which 72.6% (109) male and 26.4% (45) female patients. The serum Cystatin C ranged from 0.5 to 1.05 mg/l and

creatinine 0.7 to 1.4 mg/dl in normal person.

Serum Cystatin C levels was significantly higher in study group in comparison to control group (4.66 ± 0.76 Vs 0.69± 0.12, p<0.0001). The estimated GFR by Cystatin c equation was also significantly lower in study group in comparison to control group (9.19 ± 2.42 Vs 142.49 ± 39.15, p< 0.0001). Serum creatinine levels were significantly higher in study group in comparison to control group (5.19 ± 0.86 Vs 0.69 ± 0.12, p<0.0001). The estimated GFR by creatinine (CG) formula were also significantly lower in study group in comparison to control group (18.07 ± 4.344 Vs 107.10 ± 26.20, p< 0.0001).

The eGFR by Cystatin C equation was positively correlated with eGFR by CG formula (r=0.775, p<0.0001) in chronic kidney disease patients (group I). Cystatin C was positively correlated with creatinine (r=0.852, p<0.0001) in chronic kidney disease patients (group I). Cystatin C was negatively correlated with eGFR (r= -0.967, p<0.0001) in chronic kidney disease patients (group I). Creatinine was negatively correlated with eGFR (r= -0.871, p<0.0001) in chronic kidney disease patients (group I).

Creatinine was correlated positively with age (r=0.626, p<0.0001) in group III. The eGFR by CG formula was correlated negatively with age (r= -0.671, p<0.0001) in group III. The eGFR by CG formula was correlated positively with weight (r=0.837, p<0.0001) in group III. The eGFR by CG formula was correlated positively with age (r=0.294, p<0.001) in group IV with statistically significant difference. Creatinine was correlated positively with weight (r=0.203, p<0.05) in group IV with statistically significant difference. The eGFR by CG formula was correlated positively with weight (r=0.146, p<0.05) in group IV with statistically significant difference.

Table 1: Comparison of Biochemical Parameters between Group I and II

Parameter	Group I (n=150) (CKD patients)			Group II (n=100) Healthy control			Statistical Significance
	Min.	Max.	Mean ± SD	Min.	Max.	Mean ± SD	
Cystatin C	2.9	6.6	4.66 ± 0.76	0.50	0.90	0.69± 0.12	**p<0.0001
Creatinine	3.1	6.8	5.19 ± 0.86	0.40	0.90	0.69± 0.12	**p<0.0001
eGFR by Creatinine	12.3	29.0	18.07 ± 4.34	55.50	187.50	107.10±26.20	**p<0.0001
eGFR by Cystatin C	5.3	17.3	9.19 ± 2.42	93.00	216.00	142.49±39.15	**p<0.0001

Note: *p < 0.05 – significant, **p < 0.001 – highly significant, #p≥0.05– not significant

Table 2: Comparison of S.Cystatin C and S.Creatinine with eGFR in chronic kidney disease patients

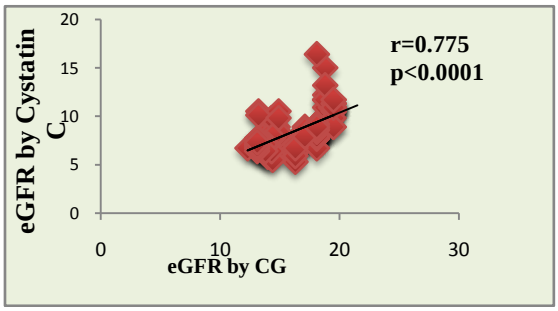
Statistics	Chronic kidney disease patients (Group I)			
	eGFR by Creatinine (ml/min/1.73m^2)	eGFR by Cystatin C (ml/min/1.73m^2)	Creatinine (mg/dl)	Cystatin C (mg/L)
Mean	18.07	9.19	5.19	4.66
Standard Deviation (SD)	4.34	2.42	0.86	0.76
Standard Error of Mean (SEM)	0.35	0.19	0.07	0.06
Minimum	12.30	5.30	3.1	2.9
Maximum	29.00	17.30	6.8	6.6
Significance	**p<0.0001		**P<0.0001	

Note: *p < 0.05 – significant, **p < 0.001 – highly significant, #p≥0.05– not significant

Table 4: Laboratory data for participants stratified by Age Groups (n = 150). Data Presented as mean ± SD.

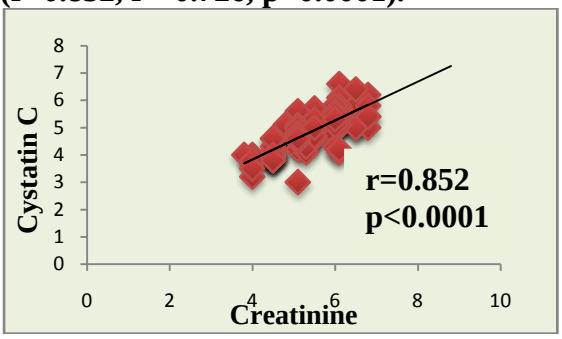
aboratory Data	Age Groups		Significance
	≤ 40 Years (Younger)	≥ 41 Years (Older)	
N	32	118	-
Age	30.59 ±5.82	50.12 ±6.02	p<0.0001
Weight	63.06 ±8.76	68.62 ±5.35	p<0.0001
Creatinine	4.45 ± 0.86	5.39 ± 0.75	p<0.0001
Cystatin C	4.03 ± 0.75	4.83 ± 0.68	p<0.0001
eGFR by CG	23.89 ±5.01	16.50 ±2.36	p<0.0001
eGFR by Cystatin C	11.37 ±2.88	8.60 ± 1.91	p<0.0001

Figure 1: Correlation between eGFR by S.Cystatin C and S.Creatinine in Chronic kidney disease patients (r=0.775, r^2=0.601, p<0.0001).



The eGFR by Cystatin C equation was positively correlated with eGFR by CG formula (r=0.775, p<0.0001) in chronic kidney disease patients (group I).

Figure 2: Correlation between S.Cystatin C and S.Creatinine in Chronic Kidney Disease patients (r=0.852, r^2=0.726, p<0.0001).



Cystatin C was positively correlated with creatinine (r=0.852, p<0.0001) in chronic kidney disease patients (group I).

DISCUSSION

Low molecular weight proteins are eliminated mainly through glomerular filtration which renders their measurements potential markers of renal function. The substances most extensively studied in this respect are α1-microglobulin, and β2- microglobulin, both of which have their limitations. Serum α1-microglobulin, which is of hepatic origin, is largely bound to IgA and albumin and thus not freely filtered. The production rate of β2-microglobulin varies considerably with immune reactions as it is a part of the histocompatibility antigen complex and produced predominantly by lymphocytes. These limitations do not apply to Cystatin C for which both a constant production rate and free glomerular filtration have been documented. It has been unambiguously proved 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. [5]

It is important to measure the renal function for all types of nephropathy. For this reason, there should be confident parameters which can evaluate the renal functions. The way of measuring the renal function is to measure the glomerular filtration rate. In this study, the glomerular filtration rate measured by creatinine from CG method and Cystatin C equation. Other agents like endogen and exogen can be used and measure GFR. Endogen agents such as urea, creatinine and Cystatin C, whereas exogen agents such as inulin, iohexol, iothalamate, ethylenediamine tetraacetic acid (EDTA) and diethylene triamine pentaacetic acid (DTPA) can be used. In the assay of GFR, gold standard is the measurement of the exogen agents. While inulin clearance is considered to be the gold standard for measurement of GFR, its use in the clinical setting is limited by multiple factors.[16]

Characteristics of an ideal Marker for GFR Measurement[16]

- Constant rate of production (for exogenous marker can be delivered intravenously at a constant rate).
- Plasma should be in a stable concentration.
- Freely filterable at the glomerulus (minimal protein binding).
- No tubular reabsorption.
- No extra renal elimination or metabolism.
- No tubular secretion
- Availability of an accurate and reliable assay
- Applicability should be practical.

Exogenous markers are safe, convenient, readily available and inexpensive and are not influence by other factor. Creatinine which is used to determine GFR is influenced by muscle mass, dietary protein intake, sex and age. Creatinine method of evaluation of GFR is susceptible to errors of its tubular secretion which can be altered by multiple factors like drugs. Even if creatinine value is normal, GFR can be low. For these reasons, search for an alternate agent still continued. Recent studies have addressed the use of other endogenous markers, such as Cystatin C, a ubiquitous nonglycosylated cysteine protease inhibitor protein that is produced at a relatively constant rate and is freely filtered by the kidneys.[16]

Kumaresan and Giri conclude that, Cystatin C seems to be a promising alternative to creatinine as an endogenous

marker of GFR in CKD patients in adults and older age groups. Serum cystatin C is directly related with GFR but not with age, and is also not influenced by BMI and body surface area, whereas serum creatinine is influenced by body mass. These findings may improve the utility of cystatin C as a laboratory diagnosis test for assessment of renal function.[5]

Observation of the present study indicate that levels of Cystatin C and creatinine were found significantly higher in group I ($p<0.0001$) as compared to control group II while difference in Cystatin c and creatinine levels between group I and II was also significant ($p<0.0001$). Both Cystatin c and creatinine were positively correlated with each other and negatively correlated with eGFR in chronic kidney disease patients group I.

The present study observed that creatinine level was not affected much by weight but eGFR CG formula was showed positive correlation by younger age group. Cystatin C levels were not affected either by age or weight. At the same time eGFR values by Cystatin equation almost unaffected by age and weight.

CONCLUSION

On the basis of present study, it is concluded that Cystatin C seems to be a promising alternative endogenous marker to creatinine for estimation of glomerular filtration rate in chronic kidney disease patients. Serum cystatin C is directly related with glomerular filtration rate but not influenced with age, sex, body weight and diet as compare to serum creatinine.

These findings may improve the utility of cystatin C as a laboratory diagnosis test for estimation of glomerular filtration rate to assess the renal function in routine clinical practice. However, in order to get more clear information broader and detailed comparative studies are required.

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