Available Online through
www.ijpbs.com (or) www.ijpbsonline.com

IJPBS |Volume 3| Issue 1 |JAN-MAR |2013|372-377

Review Article
Biological Sciences

CYSTATIN C: A BETTER INDICATOR THAN CREATININE TO ASSESS THE RENAL FUNCTIONS

Shilpasree A S*, Satya Prakash, M. Itagappa

Dept. of Biochemistry, Santosh Medical College, Ghaziabad

***Corresponding Author Email: kirancapricorn@yahoo.com**

ABSTRACT

Plasma or Serum creatinine is most widely used to measure Glomerular filtration rate (GFR) in clinical practice. Although most widely used, creatinine cannot be considered as an ideal marker due to its various preanalytical and analytical limitations. The major disadvantage of creatinine being it is unable to detect mild reduction in GFR (60-80ml/min/1.73m^2). To overcome its limitations, various creatinine based formulas have been introduced to estimate the GFR from creatinine concentration with the correction for age, muscle mass and sex. The Cockcroft and Gault (C&G) formula and modification of diet in renal disease (MDRD) formula are most commonly used in adults and Schwartz formula is used in children. However use of these formulas to estimate the GFR does not bypass inherent limitations of creatinine. Cystatin C is a low molecular weight protein used to estimate GFR. Cystatin C is considered superior to creatinine due to its various properties like constant production independent of age, sex, muscle mass and not being secreted or reabsorbed by the renal tubules. Major advantage of Cystatin C is its ability to detect mild reduction in GFR (60-80ml/min/1.73m^2). Many studies have demonstrated that cystatin C is a better marker than creatinine but few other studies have concluded that cystatin C is equivalent to creatinine but provides no advantage. So we have extensively reviewed the literature to compare the usefulness of Cystatin C over Creatinine in normal subjects as well as in individuals with Acute Renal Failure, Chronic Renal Failure, Diabetes, pediatric population and in elderly subjects.

KEY WORDS

Creatinine, GFR- Glomerular filtration rate, Cystatin C

Glomerular filtration rate (GFR) is considered as a reliable measure of functional capacity of the kidneys. It is defined as the volume of plasma that can be completely cleared of a particular substance by the kidneys in a unit of time. Clearence of a variety of exogenous and endogenous markers have been used to estimate the GFR. The "gold standard" for determining GFR is to measure the clearance of exogenous substances such as inulin, iohexol, 51Cr labeled ethylenediaminetetra-acetic acid (EDTA), 99mTc-labeled diethylenetriamine pentaacetic acid (DTPA), or 125I-labeled iothalamate. These techniques, however, are time-consuming, labor-intensive, expensive, and require administration of substances that make them incompatible with routine monitoring. Thus, the measurement of endogenous blood substances to estimate GFR is a common practice. Properties of an ideal endogenous blood substance to estimate GFR should include release into the blood stream at a constant rate, free filtration by the glomerulus, no reabsorption or secretion by the renal tubules, and exclusive elimination via the kidneys.[1]

Most widely used endogenous marker for GFR is creatinine expressed either as its plasma concentration or renal clearance. Creatinine

fulfills most, but not all of the requirements for a perfect filtration marker. It is a low molecular weight substance, not protein bound; freely filtered, not metabolized by the kidney and it is physiologically inert.[2]

Nevertheless, serum creatinine remains a crude marker of GFR because its concentration is affected by various factors like age, gender, muscle mass, exercise, nutritional status etc.[3] Serum creatinine is also insensitive for detecting small decreases in GFR (60-80 ml/min/1.73m^2) because of the nonlinear relationship between its plasma concentration and GFR. [2] A small but significant proportion of creatinine is excreted in the urine is derived from tubular secretion. This leads to overestimation of the GFR. Further, the proportion of total renal creatinine excretion due to tubular secretion increases with decreasing renal function. This amplifies the overestimation of GFR. Tubular secretion of creatinine is not constant and varies, not only within an individual, but between individuals.[4,5]

Several substances can interfere with laboratory measurements of creatinine. Glucose, uric acid, ketone bodies, plasma proteins, and cephalosporins may lead to falsely high creatinine values when the Jaffe colorimetric method is used [6]. Creatinine clearance determinations involving timed urine collections may provide greater accuracy but are difficult for patients to perform, time-consuming, and impractical for routine use. Inaccuracies may still arise if the specimens represent “under-” or “over”collections. Many creatinine based formulas have been introduced to estimate the GFR from creatinine concentration with the correction for age, muscle mass and sex. The Cockcroft and Gault (C&G) formula and MDRD formula are most commonly used in adults and schwartz formula is used in children. [1] However these formulas developed for estimating creatinine clearance in healthy men, may not be appropriate for estimating creatinine clearance in women or in patients with renal disease and the use of formulas to estimate creatinine clearance does not bypass inherent limitations of creatinine as a filtration marker.[2]

Eventhough creatinine is most commonly used to assess the renal functions, due to its various limitations the search for ideal marker continues. Cystatin C is a small 13kDa protein that fulfils all the basic requirements for an endogenous filtration marker.[1] Cystatin C is produced by all nucleated cells at a constant rate, regulated by a so-called housekeeping’ gene. The production rate of cystatin C is remarkably constant over the entire lifetime and elimination from the circulation is almost completely via glomerular filtration. In the absence of significant tubular damage, cystatin C is reabsorbed and metabolised by the proximal tubular epithelial cells and is not returned to the circulation.The cystatin C plasma concentration is independent of the muscle mass. Thus, the strong association with sex age and Muscle mass seen with creatinine is not observed for cystatin C. The increase of cystatin C with ageing (>50 years of age) reflects the natural decrease of renal function in advanced age. Only a few circumstances have been identified that have an impact on cystatin C plasma concentration: High-dose glucocorticoid therapy and Thyroid dysfunction. Many studies have confirmed the high sensitivity and specificity of Cystatin C for glomerular filtration rate (GFR) estimation; in most studies cystatin C was clearly superior to creatinine with regard to renal function assessment.[7] So the purpose of this review is to compare the efficiency of cystatin C with the creatinine to assess the renal functions in different population groups including normal subjects and patients with Acute Renal Failure, Chronic Renal Failure, Diabetic nephropathy, Pediatric patients and in elderly individuals.

Various studies have shown the usefulness of cystatin C to assess the GFR. Frans J. Hoek et al compared the diagnostic accuracy of cystatin C with creatinine and creatinine based Cockcroft and Gault (C&G) formulafor estimation of GFR. The area under the curve (AUC) of the receiver operating curves (ROCs), a measure of diagnostic accuracy, for cys C (0.931) and C&G (0.938) were equal (P 0.815) and both better than the creatinine AUC (0.848; P 0.006). The day-to-day variation (biological and analytical) for cys C was small in diabetic patients. In the follow-up study in diabetic patients, cys C was the parameter which had the best correlation (r 0.66) with changes in GFR. Cys C gave a good estimate of GFR, more accurate and precise than C&G formula.[8]

In a study conducted by Stefan herget-rosenthal,et al among 85 patients at high risk to develop ARF,44 patients developed ARF and 41 served as controls. ARF was defined according to the Risk of renal dysfunction, Injury to the kidney, Failure of kidney function, Loss of kidney function, and ESRD (RIFLE) criteria. The increase of cystatin C significantly preceded that of creatinine. Specifically, Serum cystatin C increased already by ≥50% 1.5 ± 0.6 days earlier compared to creatinine. Serum cystatin C demonstrated a high diagnostic value to detect ARF as indicated by area under the curve of the ROC analysis of 0.82 and 0.97 on the two days before the criteria was fulfilled by creatinine. Cystatin C detected ARF with a sensitivity of 55% and 82% on these days respectively. Since there is absence of effective, specific therapies for ARF, the early and accurate detection of ARF by using cystatin C is crucial to prevent its progression, and thereby, to potentially improve its outcome.[9]

Ahlström A et al showed that among 202 patients admitted to intensive care unit 54(27%) patients developed ARF. Serum Cystatin C showed excellent positive predictive value for ARF in critical illness by ROC analysis. Abnormal values of serum Cystatin C and plasma Creatinine appeared equally quickly (median 3 days). Serum Cystatin C was as good as plasma Creatinine but neither marker was clinically useful in predicting mortality [10]

In a study conducted by Tarif N et al in 73 patients with ARF and 300 healthy individuals, Cystatin C correlated significantly with serum Creatinine and estimated GFR and this correlation was much greater in patients with deteriorating renal functions than in patients with improving renal functions. Hence cystatin c is a good marker of renal functions in ARF patients with worsening renal functions [11]

Many studies have been conducted to study the usefulness of cystatin c in progression and staging of chronic kidney disease (CKD). Katharina-Susanne Spanaus et al did follow up of 177 patients with non diabetic chronic kidney disease for 7 years. 65 patients had a progressive CKD These patients were older and had a lower GFR and higher serum Creatinine, and Cystatin C values at baseline (all P <0.001) compared with the patients who did not progress. Cox proportional hazard regression analysis revealed that both clearance markers were equally strong predictors of CKD progression, even after adjustment for age, sex, GFR, and proteinuria.[12]

In a study conducted by Shani Shastri, MD et al Cystatin C level was a risk factor for incident CKD stage 3 and added information beyond that provided by baseline GFR estimated from serum Creatinine .This was attributed to two reasons first one is Cystatin C is a better estimator of measured GFR in those with eGFR >60 mL/min/1.73 m^2, it is the range in which the Creatinine based equations are less accurate. Alternatively, Cystatin C level reflects other factors independent of measured GFR that are associated with kidney disease progression [13]

Lesley A. Stevens, et al estimated GFR using Creatinine alone and using Cystatin C with Creatinine in 3408 patients with CKD. GFR was estimated using the 4 new equations based on serum Cystatin C alone, serum Cystatin C, serum Creatinine, or both with age, sex, and race. Serum Cystatin C level alone provided GFR estimates that are nearly as accurate as serum Creatinine level adjusted for age, sex, and race, thus providing an alternative GFR estimate that is not linked to muscle mass.[14]

Danilo Fliser, MD et al showed that Serum cystatin C concentration is a better marker of renal dysfunction than plasma creatinine concentration, at least in elderly subjects with plasma creatinine concentrations within the normal range. They studied the con of cystatin C, serum creatinine and GFR in young normotensive patients and elderly normotensive and hypertensive subjects. GFR was measured using insulin clearance. The correlation between serum cystatin C concentration and C_{In} (r = -0.65; P<0.001) was considerably better than between plasma creatinine concentration and C_{In} (r = -0.30; P<0.02).[15]

Stefan Herget-Rosenthal′ et al studied the efficiency of cystatin c as a screening test to detect reduced GFR in 226 patients with different nephropathies including glomerular and tubular damage. Cystatin C detected reduced GFR with higher sensitivity (97 vs. 83%), and higher negative predictive value (96 vs. 87%) compared to creatinine. In parallel, sensitivity of cystatin C as derived from receiver-operating characteristic plot was significantly higher ($p < 0.05$). In the subgroups with glomerular or tubular impairment, cystatin C and creatinine did not significantly differ with regard to efficacy.[16]

Diabetes mellitus due to its various microvascular and metabolic complecations has multiple effects on renal functions and creatinine metabolism. Studies in patients with type 1 and type 2 DM have demonstrated 25 to 50% increase in GFR compared to normal subjects. Long-standing diabetes mellitus is associated with the development of renal failure in 30-50% of type 1DM patients and in 5% of type 2 DM patients. Detecting the early decrease in renal function in diabetic nephropathy by means of the serum creatinine concentration is difficult because of initially increased GFR and creatinine clearance and the lack of precision of measurements of serum creatinine within the normal range. As in other forms of chronic renal disease, the serum creatinine concentration is insensitive for detecting decreased GFR in Diabetic nephropathy.[2]

Michele mussap et al compared diagnostic accuracy of serum cystatin C and creatinine for estimating GFR in 52 patients with type 2 DM. The overall reciprocal relationship between cystatin C and GFR was significantly stronger (r - 0.84) than those between serum creatinine and GFR (r - 0.65) and between Cockcroft and Gault estimated GFR and GFR (r - 0.70). Diagnostic accuracy of serum cystatin C (90%) was significantly better than those of serum creatinine (77%) and Cockcroft Gault estimated GFR (85%) in discriminating between type 2 diabetic patients with normal GFR (>80 ml/min per 1.73 m2) and those with reduced GFR (<80 mL/min/1.73 m^2). So serum cystatin C may be considered as more accurate marker in discriminating type 2 diabetic patients with reduced GFR from those with normal GFR.[17]

CysC has advantage over SCr in pediatric populations because of the low muscle mass in children, which leads to very low SCr values, where increased assay imprecision is present. Therefore, it is difficult to accurately detect small changes in GFR with SCr in children. On the other hand, the plasma concentration of CysC appears to be constant in children >1 year of age and similar to that of adults .[18, 19]

Guido Filler et al assessed the diagnostic accuracy of Beta trace protein and compared with cystatin C, Beta 2 microglobulin and creatinie in 225 children with various renal pathologies. The reciprocal correlation of GFR with BTP, Cystatin C, and the Schwartz GFR estimate were significantly higher (r =0.653, 0.765, and 0.706, respectively; P <0.05) than with the reciprocal of creatinine or β2-MG (r =0.500 and 0.557, respectively). ROC analysis showed a significantly higher diagnostic accuracy of BTP, Cystatin C, and Schwartz GFR estimate for the detection of impaired GFR than serum creatinine (P <0.05). [20]

CONCLUSION

From the extensive review of various publications, cystatin C is considered as a better indecator of renal functions than creatinine both in healthy subjects and in patients with impaired renal functions. This is due to the unique properties of cystatin C like constant production independent of age, sex, and muscle mass and not being secreted or reabsorbed by the renal tubules. The major advantage of cystatin C over creatinine is its ability to detect mild reduction in GFR to which creatinine is insensitive. Since there are no specific therapies, early detection of impaired renal functions is crucial to prevent the progression of renal disease and to improve the patient outcome. The main disadvantage of cystatin C being high cost of its immunoassay. Although all the studies reviewed here have demonstrated the distinct advantage of cystatin C over creatinine it is important to document the advantage of cystatin C to improve the patient outcome. Replacement of creatinine which is most widely used from a new marker cystatin C ultimately depends on the results of patient outcome studies.

REFERENCES

1. Delany MP, Price CP and Lamb EJ. Kidney function and disease. In: Brutis CA Ashwood ER and Bruns DE eds. Teitz fundamentals of clinical chemistry, 6th edn. Philadelphia : WR Saunders Co; 2008: p631-654
2. Perrone RD, Madias NE and Levey AS. Serum Creatinine as an Index of Renal Function: New Insights into Old Concepts. Clin Chem 1992;38(10); 1933-1953
3. James GD, Sealey JE, Alderman M, Ljungman S, Mueller FB, Pecker MS, Laragh JH. A longitudinal study of urinary creatinine and creatinine clearance in normal subjects: race, sex, and age differences. Am J Hypertens 1988;1:124–131
4. Swan SK. The Search Continues—An Ideal Marker of GFR. Clin Chem 1997;43(6); 192-194
5. Levey AS, Berg RL, Gassman JJ, Hall PM, and Walker WG. Creatinine filtration, secretion and excretion during progressive renal disease. Modification of Diet in Renal Disease (MDRD) Study Group. Kidney Int Suppl. 1989; 27:S73-80.
6. Gerard SK, Khayam-Bashi H. Characterization of creatinine error in ketotic patients: a prospective comparison of alkaline picrate methods with an enzymatic method. Am J Clin Pathol 1985; 84:659–64.
7. Carola Wagner. Cystatin C, Renal Function and Cardiovascular Risk. European Nephrology, 2010;4:49–54
8. Hoek FJ, Kemperman FAW and Kridiet RT. A comparison between cystatin C, plasma creatinine and the Cockcroft and Gault formula for the estimation of glomerular filtration rate. Nephrol Dial Transplant (2003) 18: 2024–2031
9. Rosenthal SH, Marggraf G, Hosing J, Goring F and Pietruck F et al. Early detection of acute renal failure by serum cystatin C. Kidney International 2004; 66; 1115–1122
10. Ahlström A, Tallgren M, Peltonen S, and Pettilä V. Evolution and predictive power of serum cystatin C in acute renal failure. Clinical Nephrology 2004;62 (5);344-350
11. Tarif N, Alwakeel JS, Mitwalli AH, Durdana H and Memon NA et al. Serum Cystatin C as a marker of renal function in patients with Acute Renal Failure. Saudi J Kidney Dis Transplant 2008;19(6);918-923
12. Spanaus KS, Kollerits B, Ritz E, Hersberger M and Kronenberg F et al. Serum Creatinine, Cystatin C, and Beta Trace Protein in Diagnostic Staging and Predicting Progression of Primary Nondiabetic Chronic Kidney Disease. Clinical Chemistry 2010; 56(5) 740–749
13. Shastri S, Katz R, Shilpak MG, Kestenbaum B and Peralta CA et al. Cystatin C and Albuminuria as Risk

Factors for Development of CKD Stage 3. Am J Kidney Dis. 2011;57(6):832-840.
14. Stevens LA, Coresh J, Schmid CH, Feldman HI and Froissart M et al Estimating GFR Using Serum Cystatin C Alone and in Combination With Serum Creatinine: A Pooled Analysis of 3,418 Individuals With CKD. American Journal of Kidney Diseases 2008; 51(3);395-406
15. Fliser D and Ritz E. Serum cystatin C concentration as a marker of renal dysfunction in the elderly. Am J Kidney Dis. 2001 ;37(1):79-83.
16. Herget-Rosenthal s, Trabold s , Pietruck F, Holtmann M, Philipp T et al Cystatin C: Efficacy as Screening Test for Reduced Glomerular Filtration Rate. Am J Nephrol 2000;20:97-102
17. Mussap M, Vestra M, Fioretto P, Saller A,and Varagnolo M et al. Cystatin C is a more sensitive marker than creatinine for the estimation of GFR in type 2 diabetic patients. Kidney International 2002; 61; 1453–1461
18. Randers E, Krue S, Erlandsen EJ, Danielsen H, Hansen LG. Reference interval for serum cystatin C in children. Clin Chem1999; 45:1856–8.
19. Bo¨kenkamp A, Domanetzki M, Zinck R, Schumann G, Byrd D, Brodehl J. Cystatin C—a new marker of glomerular filtration rate in children independent of age and height. Pediatrics 1998;101: 875–81.
20. Filler G, Priem F, Lepage N,Sinha P and Vollmer I et al. Beta Trace Protein, Cystatin C, Beta 2-Microglobulin, and Creatinine Compared for Detecting Impaired Glomerular Filtration Rates in Children. Clinical Chemistry 2002; 48(5)729–736

***Corresponding Author:**
Dr. Shilpasree A S
Assistant Professor
Dept. of Biochemistry
Santosh Medical College,
Santosh Nagar, Pratap Vihar, Ghaziabad (U.P) Pin- 201009