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Review Article

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CLINICAL USEFULNESS OF CREATININE AND CYSTATIN C- AN UPDATE

Fredrick Saron[1], Dhananjayan R.[2], Swaminathan S.*[3]

[1]Lab Technologist, Dept. of Biochemistry, Apollo Speciality Hospitals, Vanagaram, Chennai – 600 095
[2]Consultant, Dept. of Biochemistry, Apollo Speciality Hospitals, Vanagaram, Chennai – 600 095
[3]Sr. Consultant and Head, Dept. of Biochemistry, Apollo Speciality Hospitals, Vanagaram, Chennai – 600 095

***Correspondence for Author: Dr. Swaminathan S.**
Sr. Consultant and Head, Dept. of Biochemistry, Apollo Speciality Hospitals, Vanagaram, Chennai – 600 095.

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ABSTRACT

According to World Health Organization, the number of people affected with kidney failure worldwide is around 10% and annually about one million people die due to untreated kidney disease. The contributing factors for kidney diseases include untreated hypertension and type 2 diabetes mellitus (T2DM). The first line of biomarker to detect kidney failure is the measurement of serum creatinine and the detection of proteins in urine and once both are elevated, the next stage is to measure Creatinine Clearance (Cr-Cl) by using serum and urine creatinine to calculate Glomurelur Filtration Rate (GFR). Recently, Cystatin C (CysC) has emerged as an alternate marker to serum Creatinine (Sr-Cr). The aim of this review article is to bring into focus the merits and demerits of using estimated GFR (eGFR), based on Sr-Cr and CysC values as preliminary to aid clinicians in the diagnosis of Kidney related diseases.

KEY WORDS: Cystatin C, Creatinine, Glomerular Filtration Rate, eGFR, Cr-Cl.

INTRODUCTION

Sr-Cr has been the traditional biomarker to assess the degree of renal damage and is still being used now based on the fact that its measurement is easy and inexpensive. CysC is a protein, the concentration of which is remarkably constant and is mainly used as a biomarker for kidney function. Recent studies indicate that CysC is a better marker for eGFR than Sr-Cr. Measuring GFR in every patient is not practical in clinical care or large epidemiologic studies. Therefore to estimate GFR, the endogenous markers Sr-Cr and CysC may be used. The use of both CysC and Sr-Cr to determine eGFR improves accuracy, but the effect on detection, staging and risk classification of Chronic Kidney Disease (CKD) across diverse populations has not yet been determined. CysC can be used as an alternative to Sr-Cr and Creatinine - Clearance (Cr-Cl) to screen for and monitor kidney dysfunction in those with known or suspected kidney diseases. CysC is encoded by the CST3 gene and is mainly used as a biomarker of kidney function. It has a low molecular weight, and it is removed from the blood stream by glomerular filtration in the kidneys. If kidney function and GFR decline, the blood levels of CysC rise. Various studies state that it is an early and sensitive marker for CKD. In this review article we have presented the recent research findings on the clinical usefulness of Sr-Cr and CysC.

Measurement of GFR is crucial for the detection and follow-up of an early renal impairment. Inulin clearance or radio-isotopes are the gold standards but they are difficult for routine use. Sr-Cr and Cr-Cl are the most widely used, but they lack sensitivity to detect an early renal impairment in cases of obesity, malnutrition and advanced age. Looking for a more reliable marker is necessary and CysC seems to be an alternate to Sr-Cr. This molecule is constantly produced by nucleated cells, then freely filtered and catabolized in the proximal tubule. Clinical studies showed that CysC might be a more reliable marker of GFR in determined groups of patients. Moreover this molecule may have another interest as a predictive risk factor or mortality, especially for cardiovascular events.[1]

The albumin: creatinine ratio (ACR) is a better surrogate for Albumin Excretion Rate (AER) than absolute albumin concentration. If 'action levels' are to be defined for screening programmes, they should be derived from diabetic and not non-diabetic data and should be different in men and women. It could be good if a direct rather than screening role for the ACR in the management of diabetic nephropathy is formulated.[2] Taking into account age and gender, the Blood Urea Nitrogen (BUN)/Cr ratio correlated significantly with an upper Gastro Intestinal source of bleeding, with a ratio greater than 36 having a sensitivity of 90% and a specificity of 27%. The area under the receiver operating characteristic curve (ROC) using age, gender and BUN/Cr ratio was 0.73 (95% confidence interval, 0.62 to 0.84).[3]

Biochemical characteristics include changes in Sr-Cr and its concentrations in body fluids. Guanidinoacetate methyltransferase (GAMT) and Arginine-Glycine AmidinoTransferase (AGAT) deficiency are treatable by oral Cr supplementation, while patients with Creatine Transporter (CRTR) deficiency do not respond to this type of treatment. The Cr deficiency syndromes are under diagnosed, so their possibility should be considered in all children affected by unexplained mental retardation, seizures and speech delay.[4] GAMT and AGAT deficiencies are treatable by oral Cr supplementation, but patients with Cr transporter deficiency do not respond to this type of treatment.[5]

A positive correlation was observed between GFR based on Sr-Cr and CysC among the diabetic CKD patients. Sr-Cr and CysC were significantly correlated with body weight and muscle mass, but the strengths of these correlations were greater for Sr-Cr. Despite the strong correlation between Sr-Cr and CysC, CysC is less affected by weight and muscle mass and could represent a better alternative for the assessment of renal function.[6] CysC may be considered as an alternative and more accurate serum marker than Sr-Cr or the Cockcroft and Gault (CG) eGFR in discriminating T2DM patients with reduced GFR from those with normal GFR.[7]

The correlation of Sr-Cr with GFR, its diagnostic accuracy and sensitivity were significantly lower than those of CysC. A moderate reduction in GFR may be present in diabetic patients with low Sr-Cr levels. Although CG formula remains the most reliable and the less expensive tool for the evaluation of renal function, CysC is a more reliable criterion for screening and assessment than Sr-Cr and represents a useful alternative to the CG formula.[8] Clinicians should be aware of the limitations and not to overrate eGFR by single marker or calculated by equations and should not entirely rely on GFR estimates to make precise clinical decisions.[9] If CysC, which is clearly more expensive, is used, the choice of the CysC determination method and an adjusted prediction equation is essential. Use of the Isotope Dilution Mass Spectrophotometry (IDMS)-traceable Modification of Diet in Renal Disease (MDRD) seems to yield the best cost-benefit ratio for routine practice.[10]

The ROC plot indicates that CysC is superior to Sr-Cr and Cr-Cl for detecting impaired GFR. Serum CysC appropriately reflects GFR in diabetes, and is more efficacious than Sr-Cr and Cr-Cl in detecting reduced GFR in T2DM patients.[11] Sr-Cr, GFR-Diethylene Triamine Para Acetic acid and Cr-Cl were not different between both diabetic groups and controls. CysC was positively correlated with beta 2-microglobulin and Sr-Cr in microalbuminurics and negatively with GFR. A significant inverse correlation was found between beta2-microglobulin and GFR in both microalbuminurics and normoalbuminurics. Increased CysC and beta2-microglobulin in diabetics may be early indicators of incipient Diabetic Nepropathy (DN). The diagnostic accuracies of CysC and beta2-microglobulin are superior to that of Sr-Cr in distinguishing between mild and moderately reduced GFR.[12]

The combined Sr-Cr-CysC equation performed better than equations based on either of these markers alone and may be useful as a confirmatory test for CKD.[13] The diagnostic performance of CKD-Epidemiological Collaboration (CKD-EPI) Cr-CysC equation in patients with cirrhosis was superior to conventional equations in clinical practice for estimating GFR. However, its diagnostic performance was substantially worse than reported in subjects without cirrhosis.[14]

The assessment of renal function is of vital importance in the management of patients with cirrhosis. While Sr-Cr is routinely used for this purpose, Cr based eGFR does not reflect true renal function because of muscle wasting and impaired liver function. CysC based eGFR to assess renal function and predict outcome more accurately compared with Cr-based eGFR in cirrhotic patients.[15] CysC level was the only independent predictor for significant renal impairment. Significant renal dysfunction was not rare in patients with cirrhotic ascites, even their Sr-Cr level is normal and CysC is a useful marker for detecting significant renal dysfunction in these patients.[16] CysC based eGFR can identify a reduced GFR more accurately than Sr-Cr based formula. CysC >1.09 mg/L (i.e. eGFR<60 mL/min/1.73 m^2) could be a marker of a reduced GFR, and CysC >1.365 mg/L would strongly suggest a reduced GFR in patients who have rheumatoid arthritis with secondary amyloidosis.[17] Both Sr-Cr and CysC are highly inaccurate markers of renal function in advanced chronic renal failure patients.[18]

Elevated C-reactive protein and white blood cell count and lower serum albumin were associated with higher levels of CysC and lower levels of Sr-Cr. Adjustment for age, gender and race had a greater effect on the association of factors with Sr-Cr than CysC. Hence, CysC is affected by factors other than GFR which should be considered when the GFR is estimated using serum levels of CysC.[19] Meta-analysis using currently available data indicates that serum CysC is clearly superior to Sr-Cr as a marker of GFR measured by correlation or mean ROC-plot.[20]

Measurement of CysC may be useful to estimate GFR, especially to detect mild reductions in GFR, and therefore may be important in the detection of early renal insufficiency in a variety of renal diseases for which early treatment is critical.[21] Urine Cortisol to Creatinine Ratio is significantly associated with renal dysfunction, the severity of Metabolic Syndrome (MS), arterial stiffness and weight change in obese patients. Available data suggest that U-CysC could serve as a marker for Cardio Vascular Disease (CVD) and

CKD risk factor in patients with obesity and MS.[22] The decrease in Cr-Cl with age seen in a study represents true renal ageing and is not secondary to diseases which become increasingly prevalent in the elderly. A nomogram constructed from these data provides normative age-corrected standards for Cr-Cl.[23]

Smoking, low High Density Lipoprotein cholesterol (HDLc) and higher diastolic blood pressure were associated with higher CysC levels. Non-diabetics without overt vascular disease exhibit an age related but heterogeneous decline in renal function. The ageing effect is more pronounced in men. At least half of healthy 80+ years old could be expected to have at least CKD Stage 3 with eGFR < 60 ml/min/1.73 m^2.[24] Diet has an important influence if meat intake is substantial or if consumption of a creatine-free diet is prolonged. Cr metabolism and extra renal excretion are minor, except in subjects with reduced renal function. Application of a correction for constant extra renal clearance of Cr in patients with CKD probably is not valid. Further observations of Cr excretion in normal subjects of varying age and height are needed.[25]

A significant difference was noted regarding the Cr/CysC ratios between patients with Non Small-Cell Lung cancer (NSCLC) and those with Small-Cell Lung Cancer (SCLC). A significant difference was also noted in the Cr/CysC ratios for patients with NSCLC with toxicity grades <3 and ≥3. Similar findings were observed in patients with NSCLC who received platinum-based combination therapy.[26] Addition of eGFR by the combined Cr-CysC equation yielded AUCs of 0.6923 (Gentian) and 0.6924 (Roche) with relative integrated discrimination improvement (IDI) values of 3.54% and 3.24%. Despite differences in CysC concentrations, overall correlation between the Gentian and Roche assays was good, while agreement was moderate. The combined Cr-CysC equation did not outperform risk prediction by CKD-EPI.[27]

CysC seems to reflect contrast media-induced changes in kidney function better than Sr-Cr. N- Acetyl Cysteine (NAC) and Zn have no effect in preventing Contrast Induced Nephropathy (CIN) by the standard definition, but based on CysC we can confirm a preventive effect of NAC. It appears mandatory to assess kidney function by CysC in CIN intervention trials, because relying only on Sr-Cr may be misleading.[28] A multivariate analysis of covariance showed that lean mass was significantly related to serum and urinary Cr but not with Cys, even after adjustment for protein/meat intake and physical activity. CysC may represent a more adequate alternative to assess renal function in individuals with higher muscle mass when mild kidney impairment is suspected.[29] Prospectively measured Sr-Cr, within normal ranges, is positively related to prostate cancer risk. Future research should re-examine the association in other populations, including any interrelationship with serum prostate-specific antigen.[30]

Cr-Cl systematically over estimates GFR in healthy subjects and this over estimation significantly correlates with BMI, with higher fractional excretion of Cr in subjects with higher BMI. The impact of BMI on tubular Cr secretion can be accounted for, when using Cr-Cl for GFR assessment in the normal to high range, by the following formula: GFR = 24-h CrCl - (22.75 + 0.76 × BMI - 0.29 × mean arterial pressure (-6.11 if female).[31] Measurement of CysC , has been suggested for use as an indicator of GFR in a manner analogous to the use of Sr-Cr.[32] The CysC increase also was detectable with raw Cerebro Spinal Fluid (CSF) or after antibody capture. These data are consistent with previous animal study and the idea that persistent pain induces the synthesis and release of CysC in dorsal spinal cord, the surplus of which overflows into the CSF.[33]

The CysC level was significantly lower in the combined group of G/A and A/A genotypes compared with G/G. Some data demonstrate that the level of CysC in CSF should not be considered as a biomarker of Amyotrophic Lateral Sclerosis (ALS), but there is a correlation between CysC levels and the CST3 genotype.[34] Albuminuria and impaired GFR were independent, additive risk factors for mortality among older adults with diabetes. These findings support current recommendations to regularly assess both albuminuria and GFR in the clinical care of patients with diabetes; a focus on interventions to prevent or treat CVD in the presence of albuminuria, impaired GFR, or both; and further consideration of CysC use in clinical care.[35]

Renal dysfunction is a risk factor for cardiovascular events in patients with atherosclerosis. Unlike Sr-Cr or eGFR, CysC reflects renal dysfunction independent of factors such as sex, weight, and race. Cr levels showed no significant association with major cardiovascular events. CysC was significantly and gradually associated with future cardiovascular events in patients with carotid atherosclerosis. In contrast, neither Sr-Cr nor eGFR were significant predictors of adverse cardiovascular outcomes.[36] Kidney function monitoring using Cr-based GFR estimation is a routine part of clinical practice. Emerging evidence has shown that CysC may improve classification of GFR for defining CKD in certain clinical populations and assist in understanding the complications of CKD.[37]

Combined analysis of CysC and NT-pro BNP could provide important prognostic information among elderly patients in the community with symptoms of Heart failure (HF).[38] CysC was a stronger predictor of adverse events than conventional measures of kidney function. In addition, CysC offered complementary prognostic information to cardiac biomarkers and could help clinicians perform more accurate risk stratification

of patients with acute HF[39]. The association between and the combined end point of death or rehospitalization during 1-year follow-up remained significant after adjusting for age, race, gender, co-morbidities, and Sr-Cr. CysC was more predictive of these end points than Sr-Cr and the combination of CysC and Sr-Cr was more predictive than either variable alone. CysC may be useful in addition to Sr-Cr for predicting outcomes after admission for acute HF exacerbations.[40] Both systolic blood pressure and pulse pressure were significantly associated with kidney function across a wide range of CysC concentrations, even in subjects with presumably normal kidney function, by Cr-based measures. CysC may provide new insights into the association of CKD and hypertension, a relationship that may be an underappreciated barrier to hypertension control.[41]

CONCLUSION

CysC may be used as an alternative to Sr-Cr and Cr-Cl to screen for and monitor kidney dysfunction in those with known or suspected kidney disease. It may be especially useful in those cases where Sr-Cr measurement is not appropriate, for instance, in those who have liver cirrhosis, obese, malnourished or have reduced muscle mass. The use of CysC alone or in combination with Sr-Cr strengthens the association between the eGFR and the risks of death and End-Stage Renal Disease across diverse populations. CysC can be measured in a random sample using immunoassays. Even though it is a more expensive test than Sr-Cr, CysC is a more accurate test for kidney function than Sr-Cr . Further studies are required, especially on cost effective assay for CysC, so that it could be introduced in clinical laboratories as routine test along with Sr-Cr and may be used in selective group of patients, such as, those with cirrhosis, obese and CVD

Conflict of Interest None

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