

Cystatin C -a Promising Marker of Glomerular Filtration Rate

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ABSTRACT

Glomerular filtration rate (GFR) is the best single measure of overall function of kidney. GFR is routinely assessed by measuring the concentration of endogenous serum markers such as blood urea nitrogen and serum creatinine (SCr). Although widely used these endogenous marker are not ideal and do not perform optimally in certain clinical settings. The purpose of this review is to critically review the potential utility of Cys C as a new promising markers of GFR and to review whether Cys C had any advantage over routinely used endogenous marker in different population group.

Key Words: Glomerular Filtration Rate (GFR), Serum Creatinine (Scr), Blood Urea, cystatin C (Cys C)

Introduction

Glomerular filtration rate is defined as the volume of plasma that can be completely cleared of a particular substance by the kidneys in a unit of time¹. GFR is the sum of filtration rate of all functioning nephrons. GFR can be measured only indirectly². The gold standard for determining GFR is to measure the clearance of exogenous substance such as inulin, iothalamate, ⁵¹Cr- EDTA, ⁹⁹Tc-labeled diethylenetriamine penta acetic acid (DTPA), or ²⁵I labeled iothalamate. These techniques, however, are time-consuming, labour- intensive, expensive, and require administration of substances that make them incompatible with routine monitoring. Thus the measurement of endogenous substance is a common practice. Properties of 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 renal tubules, and exclusively eliminated by the kidneys³.

Blood urea was the first endogenous marker to assess renal function¹. Urea is freely filtered by the glomerulus and not secreted by the tubules. Limitation of urea as a GFR marker is its

passive reabsorb and its return to blood stream. Thus serum urea concentration will under estimate GFR. Furthermore, its concentration in blood can vary with diet, hepatic function, and numerous diseases states⁴.

Serum creatinine is widely used as an indirect marker to assess GFR⁵. But serum creatinine concentration is affected by factors that are independent of GFR, such as age, race, muscle mass, gender, medication use, and catabolic state⁶. Moreover, serum creatinine concentrations are insensitive to mild to moderate reductions of GFR⁷. In addition measurement of creatinine by the common Jaffe methods is subject to numerous analytical interferences due to presence of non-creatinine chromogen such as bilirubin, ketones, uric acid and some antibiotics⁸. Serum creatinine is not reabsorbed by the kidney tubules but secreted in small amount, which are subject to intra and inter individual variation. As plasma concentration increase, tubular secretion of Scr increases, leading to over estimation of GFR⁹. Thus serum creatinine is a crude indicator of a significantly impaired renal function (<50%). Furthermore, more rapid change in glomerular

filtration are not detected by SCr¹⁰. The measurement of urinary creatinine clearance overcomes some of limitations of serum creatinine but remains inaccurate because of collection errors and changes in creatinine excretion¹¹. Several prediction equation to estimate GFR from serum creatinine and other variables (age, sex, race, body weight, albumin) is therefore recommended by kidney foundation. Mostly used equations are Cockcroft-Gault¹² and modification of diet in renal diseases (MDRD) equations in case of adult¹³. The commonly used equation for children are Schwarth and Counahan¹⁴. However, this prediction equation has not validated in subject with normal and supernormal GFR¹⁵.

Thus, despite of their common use, blood urea and serum creatinine have limitations as renal markers, and search for an ideal endogenous marker continues¹⁶. Here, we reviewed recent studies of another endogenous substance, cystatin C (Cys C) as a marker of GFR estimation.

Cystatin C as GFR marker

Cys C is a protein having MW of 13 KDa containing 122 amino acids that belongs to a family of cysteine proteinase inhibitors. It is a product of a housekeeping gene expressed in all nucleated cells and is produced at a constant rate¹⁷. Because of its smaller size and cationic nature, it is freely filtered by the glomerulus. It is not secreted, but is reabsorbed by tubular cells and subsequently catabolized so that it does not return to the blood¹⁸. Again, Cys C is not affected by age, inflammatory processes, change of body mass, nutrition, fever or gender. Thus, due to stable synthesis, lack of degradation and tubular secretion, Cys C is only influenced by renal GFR, making it an ideal endogenous marker of GFR¹⁹.

Multiple studies have validated the use of Cys C as a renal marker in adult patients²⁰⁻²⁴. In addition, two studies suggested that, Cys C was more sensitive marker than Scr for small changes in GFR^{20,24}. Recent studies further suggest that Cys C is an earlier indicator of mild renal failure²⁵⁻²⁶.

Methods for measurement of Cys C

Cys C can be measured by immunoassay. Recently automated immunoassays utilizing latex or polystyrene particles coated with CysC coated antibodies were developed. There are two different version of latex immunoassay for Cys C- one based on turbimetry- particle enhanced turbimetric immunoassay (PETIA)^{27,28,29} and another based on nephelometry- particle enhanced nephelometric immunoassay (PENIA)^{30,31}.

Cys C in pediatric population

Cys C has been postulated to have an advantage over Scr in pediatric population because of low muscle mass in children, which lead to very low Scr values. Therefore, it may be difficult to detect accurately, small changes in GFR with Scr in children <4 years of age in whom normal Scr values are only 0.2-0.4 mg/L. On the other hand, plasma concentration of Cys C appears to be rather constant in children >1 year of age and similar to that of adults³²⁻³⁵. These studies also showed that immediately after birth, Cys C values were approximately twice that of older children and adults but that they reaches a mean value of 0.95 mg/L by 1 to 2 months of age. Studies suggested that blood Cys C level was higher in premature infant³⁶⁻³⁸. Cys C does not cross placental barrier, so serum Cys C level in new born is not influenced by maternal serum Cys C level³⁶.

Cys C in diabetic patients

Cys C has reported to be a reliable marker of GFR in patients with mild to moderate impairment of kidney functions in both type 1 and type 2 diabetic patients³⁹. Cys C is a better indicator than creatinine in diabetic patients and showed good correlation with changes in GFR over two years, making it a useful measure for follow up of patients with diabetes⁴⁰. Even Cys C can detect renal involvement earlier than microalbuminuria in type 1 diabetes⁴¹.

Cys C in renal transplantation

Serum Cys C determination is used for rapid and accurate assessment of renal function in patients with renal transplant. Acute rejection or infections, both are common problems in patients with renal transplants. Cys C continues to provide a precise assessment of GFR while creatinine would vary dramatically. Thus Cys C allows early recognition and accurate dosing of different immunosuppressive drugs⁴².

Cys C in acute kidney injury (AKI)

Cys C has been reported to increase about one to two days earlier than serum creatinine does in patients developing AKI⁴³.

Other population groups

GFR declines with age and Cys C reflects true kidney function better in older peoples as it is not influenced by muscle mass.

Patients with advanced cirrhosis who have an abnormal GFR can present with normal Scr values because of their decreased muscle mass and abnormal excretion of creatinine^{44,45}. But Cys C may be a better marker in cirrhotic patients⁴⁶.

In obstretrics, pre-eclamptic patients with altered kidney functions are more likely to be detected by Cys C than serum creatinine estimation⁴⁷.

On conditions ccurate estimation of GFR is essential for diagnosis, staging and management of chronic kidney diseases. Cys C is clearly an attractive endogenous marker to assess renal function. The advantage of Cys C as an earlier marker of mild damage as reported in most studies is due to several unique properties of Cys C compared with creatinine. The most of these are, its constant production, it is independent of muscle mass, age or sex and lack of its renal secretion or reabsorption back into the blood stream. Cys C is also more sensitive marker than serum creatinine in case of children and also older groups. Cys C is superior to creatinine in estimating GFR in other patients

groups such as kidney transplant, diabetic patients and cirrhotic patients with CKD etc. So, this review suggests that Cys C can detect GFR more accurately than serum cratinine can.

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