Journal of Clinical Laboratory Analysis 18:55–60 (2004)

Commentary: Clinical Diagnostic Use of Cystatin C

Davis Massey*

Department of Pathology, Virginia Commonwealth University, Richmond, Virginia

Clinicians recognize and compensate for limitations in estimating the glomerular filtration rate (GFR) using serum creatinine (sCr) measurements by the use of timed collections and mathematical manipulations of sCr. These limitations stem from that fact that sCr is affected by nonrenal influences, including muscle mass and disease state. In addition, sCr may not be sensitive enough to detect minimal declines in GFR in those patient populations in which it is important to recognize early decline. This brief review describes the limitations of sCr, and examines the contribution that sCysC may be able to make in the early recognition of declining renal function. The physiology of CysC is presented, as are the results of clinical investigations that suggest sCysC is in many instances superior to sCr in the recognition of early decline in renal function. Certain exceptions to this are noted. J. Clin. Lab. Anal. 18:55–60, 2004. © 2004 Wiley-Liss, Inc.

Key words: cystatin C; glomerular filtration; renal function; creatinine clearance

INTRODUCTION

In a recent issue of *JCLA*, Shimuza et al. (1) presented the results of their studies comparing the usefulness of serum cystatin C (sCysC) and serum creatinine (sCr) measurement as markers of progression of diabetic nephropathy in a selected population of type II diabetics. They show by a comparison of receiver-operator characteristic (ROC) plots that sCysC is a more sensitive and specific indicator of renal dysfunction in this population compared to sCr. Others have shown a similar usefulness for sCysC in a selected type I diabetic population (2). Xu et al. (3) present their findings in validating an ELISA assay for sCysC in both healthy subjects and patients with various renal diseases. They show that sCysC measurement correlates well with the calculated creatinine (CCr) clearance. These studies supporting the clinical usefulness of sCysC as a marker of renal function, and more specifically as a marker of the glomerular filtration rate (GFR), are in keeping with those of Tomino et al. (4) published earlier in *JCLA*. Tomino's group (4) showed that sCysC is a more sensitive measure of reduction in the GFR in patients with early-stage IgA nephropathy than either sCr or CCr. These authors join the ranks of investigators and clinicians who are seeking to identify a marker of GFR that is more clinically reliable than sCr, without the necessity of resorting to more expensive and clinically less convenient gold standard means, i.e., exogenous markers such as inulin, iohexol, ^{51}Cr-EDTA, and 99mTc-DPTA.

Ideal Marker

What are the shortcomings of sCr as a marker of renal dysfunction or, more specifically, as a measure of GFR? After all, sCr has been used by nephrologists as a mainstay marker of GFR for the past 40 years, and is found as an automated laboratory test in nearly every modern hospital. It is inexpensive to measure in serum, and although it is not very sensitive as a marker of GFR, it is fairly specific. Nonetheless, there are difficulties in relying on sCr as a highly accurate indicator of GFR. It would be useful here to restate the definition of GFR and outline the qualities of the ideal GFR marker. GFR is a measure of the kidney's ability to clear a particular substance (marker) from the plasma. When highly accurate determinations of GFR are desired, clinicians may employ defined quantities of exogenously introduced markers (often radiolabeled markers) in the circulation, and measure the amount of marker recovered per unit volume of urine. Further mathematical manipulations can increase the reliability of this measurement. Understandably, if a useful endogenous marker of GFR is available, it is preferable

*Correspondence to: Davis Massey, Department of Pathology, Virginia Commonwealth University, P.O. Box 980662, Richmond, VA 23298-0662. E-mail: Damassey@hsc.vcu.edu

Received 6 February 2003; Accepted 4 April 2003
DOI 10.1002/jcla.10098
Published online in Wiley InterScience (www.interscience.wiley.com).

to simply measure its concentration in serum. Historically, this marker has been creatinine, the metabolic product of creatine and phosphocreatine. Creatinine is produced in muscle, and as such is dependent on muscle mass. The ideal sensitive and specific marker should be produced endogenously and at a constant rate, regardless of age, sex, weight, diet, or disease state. It should be freely filtered and excreted by the kidney only, without renal tubular secretion, reabsorption, or modification. Once in the urine, it should remain stable until it can be measured by routinely available, cost-effective, automated means, subject to minimal analytic interference. This is a tall order to be sure, and sCr meets some, but not all, of these requirements. It does not bind plasma proteins, it is freely filtered by the kidney (although it is also secreted by the renal tubules), it is relatively specific, and its measurement is automated in nearly all hospital laboratories. However, sCr is not a sensitive marker for early decline in GFR, and analytic imprecision and bias present at low concentrations of sCr, where the earliest indications of decline in renal function occur, further reduce its sensitivity. This limits its usefulness in assessing early declines in GFR. In recognition of these limitations, and to improve the sensitivity of sCr, it is common practice to collect timed urine samples and determine CCr using a formula requiring measured sCr and urine creatinine. Obtaining accurately timed and properly collected urine samples is easier said than done. This problem has been addressed by several researchers, who have gone so far as to advocate abandoning timed collections altogether for patients entering clinical trials (5). Another mathematical manipulation of sCr, the Cockcroft-Gault formula (CGF), can improve sCr's clinical usefulness as a measure of GFR, and does not require timed urine collection. Using the CGF, which takes into account patient demographics, including age, weight, and gender, a CCr can be estimated that provides clinically useful information while avoiding the vagaries of timed urine collection. In this formula, $CCr = [(140 - age) \times \text{lean body weight in kg}]/(72 \times \text{plasma creatinine mg/dL})$. (To adjust for a lower average muscle mass in women, the product is multiplied by 0.85.) The above are additional steps and calculations intended to improve the usefulness of a GFR marker that has served adequately but may not be the best marker available.

In addition, sCr has other well-recognized limitations that are not related to its collection. Less commonly, these are independent of true changes in the GFR, and include the presence of rhabdomyolysis, and effects from eating uncooked meats or using medications such as cimetidine and trimethoprim, all of which are capable of raising sCr. A more common limitation is related to the renal tubule secretion of creatinine. Ordinarily, tubule secretion contributes relatively little to overall CCr, but as renal disease worsens and filtered creatinine declines, tubular creatinine secretion increases and becomes a relatively more significant component of CCr. Difficulties such as these have also spurred the search for a more reliable marker of GFR. Regardless of these shortcomings, identifying and monitoring renal dysfunction by determining or estimating GFR is an important and useful tool in the management of many patients, including those with diabetic nephropathy, renal or liver transplants, or other renal diseases (including the effects of hypertension). The number of articles and reviews pointing out the shortcomings of creatinine as a GFR marker, and providing strong evidence for the superiority of sCysC, continues to grow, although several knowledgeable investigators recommend caution and continued investigation (5–7).

Several other candidate GFR marker molecules have been investigated over the years, including beta(2)-microglobulin (beta(2)-M), alpha-1 microglobulin, and retinol-binding protein (8,9). However, these also fall short of the ideal because either they are not produced at a constant rate, or they are cleared by other than renal means.

History and Physiology

Clausen (10) first discovered CysC in cerebrospinal fluid in 1961, and referred to it as γ-trace. In the same year, Butler and Flynn (11) identified it in urine. Barrett et al. (12) suggested in 1984 that its physiologic function might be that of a cystine protease regulator, and proposed the name "cystatin C" for this small 13-kDa protein. CysC has shown strong promise as a suitable marker of renal function since 1985, when Simonsen et al. (13) first noted that its serum concentration correlated better with GFR than serum beta(2)-M as measured against the exogenous marker ^{51}Cr-EDTA. CysC is a member of the cystatin superfamily of cystine protease inhibitors. It is considered to be the most important inhibitor of cystine proteases, and plays a role in inhibiting lysosomal proteases. CysC is found in high concentrations in many biological fluids, including serum, urine, seminal fluid, cerebrospinal fluid, and synovial fluid (14). As the protein product of a widely distributed "housekeeping" gene expressed in all nucleated cells, it is produced at a constant rate (15), and is freely filtered by the glomerulus because of its small size and positive charge. Unlike creatinine, sCysC is not secreted by renal tubular epithelial cells, although they do reabsorb it. Once reabsorbed, it is catabolized by renal tubular epithelial cells and does not return to the bloodstream (6). sCysC levels do not appear to be affected by muscle mass (16). In the urine, CysC is

subject to degradation by the proteolytic action of microbial serine proteases. However, this degradation can be reduced by the addition of serine protease inhibitors to urine specimens (17). Refrigerated or frozen urine specimens appear to remain stable for weeks (18).

Assay

In 1979, Lofberg and Grubb (19) developed the first enzyme immunoassay for CysC. This was a competitive radial immunodiffusion assay (RIA) that enabled CysC to be detected in the serum of normal volunteers. By 1986, a double-sandwich ELISA technique had been developed for CysC measurement that gave comparable results. Both of these methods employed polyclonal antibodies. Later, Olafsson et al. (20) and Ishiguro et al. (21) separately reported the development of a monoclonal assay to detect CysC in normal human serum. Other approaches, such as automated immunoassays using latex or polystyrene beads coated with antibody to CysC, have been developed. These include a turbidometric approach (particle-enhanced turbidometric immunoassay [PETIA]), and a nephelometric immunoassay (particle-enhanced nephelometric immunoassay [PENIA]) (5,21–24). Nephelometric and turbidometric immunoassays were recently approved by the FDA, and produce consistent reference range intervals (18,25). The two methods probably have similar imprecision. In a recent review of CysC, Newman (5) examined the inter- and intrabatch precision of automated immunoassays for CysC, and compared them with those for creatinine methods. He found that imprecision in the assays is generally worse for CysC than it is for automated Jaffe and enzymatic assays for creatinine. Analytical interferences (lipemia, bilirubin, and hemolysis) are difficult to assess between methodologies, but in general the automated immunoassays for CysC appear to be less subject to interference from bilirubin, glucose, and ketones than enzymatic assays for creatinine. References ranges have been published for CysC (26,27). In general, a single reference range can be used for males and females between the ages of 1 and 50 years. At <1 year of age, CysC levels are higher than in adults, but decrease over the first year of life. At >50 years of age, sCr levels rise as the GFR declines (28).

Clinical Utility in Different Patient Populations

The diagnostic utility of CysC is becoming better appreciated, although its superiority to sCr measurement in all patient populations has not yet been clearly established. Several investigations have suggested that in patients with various renal diseases, including proteinuria and systemic lupus erythematosus, with or without steroid use, sCysC is at least as useful as sCr determination in detecting declining GFR. Kazama et al. (29) determined the GFR in 212 patients with a variety of renal diseases by means of exogenous administration and measurement of sodium thiosulfate clearance. They compared this measured GFR with the CCr, sCr, serum beta(2)-M, and sCysC. From an evaluation of ROC characteristics and the area under the curve (AUC), it was concluded that sCysC is superior to CCr when subclinical renal dysfunction is present. Likewise, Nitta et al. (30) studied GFR by measuring inulin clearance in 140 patients with various renal diseases. He also found that sCysC measurement identifies patients with mild reductions in GFR more accurately compared to sCr determination.

Recent investigations support the contention that CysC serves as reliably as sCr as a marker of renal function in elderly and pediatric populations. In both populations, low muscle mass may produce low sCr values that do not reflect true underlying GFR, and may obscure small changes in true GFR in ranges where analytical imprecision is greatest. In his ROC analysis of four approaches (sCysC, beta(2)-M, beta-trace protein, and sCr) to GFR determination in a large group of children with various renal diseases, Filler et al. (31) found that sCysC was superior to sCr in detecting mild decreases in GFR when compared to an exogenous gold standard tracer. However, using ROC analysis in studies of elderly populations, Van Den Noortgate et al. (32) found that sCysC determination did not offer improved detection of decreased GFR when compared with exogenous tracers. In contrast, Burkhardt et al. (33) measured GFR in an elderly population using inulin clearance and compared results with CCr, CGF, and sCysC. He determined that sCysC and CGF were slightly more adequate than CCr. It appears that, at least in the elderly, sCysC offers an equivalent but not necessarily superior measure of GFR.

Reduced muscle mass is also present in those with major motor spinal cord injuries, just as it may be in the elderly. Thomassen et al. (34) evaluated the clinical usefulness of sCysC determination in 24 men and women with major spinal cord injuries, as measured against sCr and determination of GFR by ^{51}Cr-EDTA. Using ROC analysis, he found that in this population sCysC was a more reliable marker of renal function than was sCr.

As shown in the article by Shimuza et al. (1), sCysC determination may be clinically useful for identifying and monitoring mild or early renal dysfunction in certain patients. Others have suggested that sCysC offers superior estimation of GFR in diabetic patients. Using a turbidometric assay for sCysC, Tan et al. (2) measured

GFR with iohexol injections in a population of type I diabetics, and compared results with GFR estimations based on sCysC, CCr, CGF, and sCr. They found that sCysC correlated with iohexol clearance as well as did CCr, and correlated better than sCr or CGF. Similarly, Mussap et al. (35) demonstrated that when compared with sCr and ^{51}Cr-EDTA, the reciprocal of sCysC correlated more strongly with GFR than did either the reciprocal of sCr or the CGF. This allowed a distinction to be made between type II diabetics with normal or slightly reduced GFR. Notably, some investigators have not detected improved sensitivity for sCysC over sCr in diabetic patients. Oddoze et al. (36) found that sCysC did not offer significantly improved GFR estimation by ROC analysis over sCr or serum beta(2)-M in 49 patients with steady-state diabetes and early renal impairment.

Investigations have also been conducted in liver and kidney transplant populations. The greater sensitivity of sCysC for early renal dysfunction may prove beneficial in renal transplant patients, in whom minor alterations of GFR may adversely affect the posttransplant course (37,38). Findings suggest that whether sCysC is superior to sCr as a measure of GFR may depend on the age of the transplanted patient (39,40). Krieser et al. (38) found no significant difference between sCysC and sCr as markers of GFR in a population of pediatric renal transplant patients, and suggested that in the light of its increased cost, sCysC offered no advantage over sCr. However, LeBricon et al. (39) evaluated changes in sCr in adult renal allograft recipients and determined that in cases of acute renal impairment, sCysC was more markedly increased than was sCr, making it a more sensitive marker of allograft function. As such, sCysC may be an early indicator of transplant rejection. In a study of 182 liver and kidney transplant patients, Hermida et al. (41) found that sCysC expressed as a ratio with sCr (sCysC/sCr) appeared to be a better marker of GFR in the liver transplant recipients than in the renal allograft recipients. However, in a study of 58 liver transplant recipients, Schuck et al. (42) found that sCysC was significantly more sensitive than sCr as a marker of GFR as compared to GFR determination by inulin clearance. They suggested that sCysC may be useful as a means of identifying recipients with minimally decreased GFR who have an apparently normal GFR by sCr measurement.

One consequence of the transplant-related immunosuppression required to prevent solid organ allograft rejection is the development of posttransplant lymphoproliferative disorder (PTLD). As a tumor marker (not as a marker of GFR), serum beta(2)-M has prognostic implications for patients with lymphoid neoplasms. However, beta(2)-M is eliminated by the kidney along with other low-molecular-weight proteins. Taking advantage of the relatively more stable serum levels of CysC during extrarenal disease, Bokenkamp et al. (43) examined the utility of the beta(2)-M/CysC ratio as a marker of lymphoproliferation. They found that the beta(2)-M/CysC ratio in healthy renal transplant patients was comparable to that found in controls, whereas in those with active PTLD the ratio was significantly elevated. Once a patient was in remission, the ratio returned to control levels.

In patients with liver cirrhosis, sCr has little practical value as a measure of GFR because it fluctuates with the severity of the disease. However, determination of GFR has important clinical implications for cirrhotic patients. Renal function tests may be used to decide when paracentesis or diuretic therapy should be instigated. Only marked impairment of GFR is reliably detected by sCr in cirrhotics; early GFR reduction may go undetected until it becomes more exaggerated. In hepatorenal syndrome, in which patients with different hepatic disorders may present with a variety of renal function abnormalities (including decreased GFR), sCr may be within the normal range even in those with very low GFR. Demirtas et al. (44) sought to determine whether sCysC could replace CCr as an indicator of GFR in patients with cirrhosis and hepatorenal syndrome. Using 99mTc-DPTA as the gold standard, they measured CCr, sCr, and sCysC in 26 patients with cirrhosis. They found that neither CCr nor sCr correlated well with 99mTc-DPTA clearance, whereas sCysC showed a higher correlation. Demirtas et al. (44) concluded that in cirrhotic patients with hepatorenal syndrome, sCysC should at least be added to a panel that includes sCr. Gerbes et al. (45) found that even for cirrhotic patients with reduced muscle mass and reduced physical activity, sCysC was better able to discriminate between a moderately reduced and a normal GFR. Similarly, Randers et al. (46) reported that the ROC characteristics for sCysC indicated greater sensitivity for reduced GFR among 36 cirrhotic patients with normal to severely impaired renal function than did sCr, when both were compared to measured CCr. In addition, Orlando et al. (47) determined the GFR in 36 cirrhotics and 56 noncirrhotic controls by measurement of inulin clearance. They found that sCysC was more sensitive in detecting early declines in GFR than either sCr or CCr. They also concluded that sCysC is a more useful measure of GFR in the cirrhotic population.

In the nonrenal setting, a significant correlation between sCysC and the risk of adverse outcome in cancer patients has been reported (48). sCysC may have additional clinical utility in the management of therapy for malignant diseases. Monitoring renal function in patients undergoing chemotherapy is crucial because

nephrotoxicity may result, along with the associated inability to eliminate chemotherapy agent metabolites. Finney et al. (25) identified no increases of sCysC in 60 patients with myeloma, and found no correlation between sCysC levels and the level of tumor paraprotein production. Others have raised questions regarding the influence of nonrenal factors on the correlation of sCysC with GFR, especially in malignant diseases. It has been suggested that sCysC increases during malignant disease progression, which makes the test unreliable as a marker of decreasing GFR in patients with growing cancers (49). Kos et al. (49) noted a significant correlation between sCysC levels and malignant disease progression in patients with melanoma and colorectal cancer. They suggested that nonrenal factors are at play in influencing the concentration of CysC in malignant sera, and that previous studies evaluating the usefulness of CysC in the serum of cancer patients may have examined an insufficient number of patients. It appears that further investigation into the usefulness of sCysC as a marker of GFR in cancer patients is required.

In a study of 48 pregnant women in the third trimester and 12 healthy, nonpregnant women, GFR was determined by iohexol clearance and compared with sCr and sCysC (50). It was found that sCysC reflected GFR as reliably as sCr in both groups.

CONCLUSIONS

On balance, sCysC determination appears to be at least as useful as (if not actually more useful than) sCr in most clinical situations requiring assessment of renal function (13,34,51,52). It appears to satisfy many of the requirements for an ideal GFR marker, and as an immunoassay it is less subject to analytical interference by bilirubin or hemolysis compared to the creatinine methodologies. However, at present, too few investigators and clinicians have been sufficiently convinced of its usefulness to make its routine use a reality. Although more study is required (especially in malignant diseases) to determine the clinical limitations of this approach, a great deal has already been accomplished in establishing a role for routine sCysC determination in many clinical situations.

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