

*Current Perspective***A New Approach for Evaluating Renal Function and Its Practical Application**Akihiro Tanaka¹, Katsuya Suemaru^{1,*}, and Hiroaki Araki¹¹Division of Pharmacy, Ehime University Hospital, 454 Shitsukawa, Toon, Ehime 791-0295, Japan

Received May 17, 2007

Abstract. In clinical practice, the measurement of endogenous serum substances in order to estimate glomerular filtration rate (GFR) is commonly performed, and the serum creatinine level has become the most commonly used serum marker of renal function. However, the measurement of the serum creatinine concentration can sometimes lead to an overestimation of GFR, especially in the elderly. In recent years, it has been suggested that GFR can be predicted based on the serum cystatin C concentrations and that the serum cystatin C concentration is not influenced by gender or age. A recent meta-analysis demonstrated that serum cystatin C is a better marker for GFR than serum creatinine. In clinical practice, it has been suggested that serum cystatin C can optimize early detection for diabetic or hypertensive nephropathy. In addition, the use of serum cystatin C is possibly more appropriate for establishing an appropriate dose adjustment of drugs that are mainly eliminated by the kidney.

Keywords: glomerular filtration rate (GFR), creatinine, cystatin C, elderly, therapeutic drug monitoring

1. Introduction

The dose adjustment of drugs eliminated by the kidney is made with respect to the degree of decrease in the renal function. Therefore, it is important to accurately estimate the patient's renal function in order to correctly adjust the dose. The glomerular filtration rate (GFR) is traditionally considered to be the best overall index of the renal function. The "gold standard" for determining GFR is to measure the clearance of exogenous substances such as inulin. However, the measurement of inulin is time-consuming, labor-intensive, and expensive, which makes it incompatible with routine monitoring. As a result, in clinical practice, the measurement of endogenous serum substances in order to estimate GFR is commonly performed. The ideal endogenous serum substance to estimate GFR should have the following properties: 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 by the kidney. The purpose of this mini-review is to review the routinely used endogenous markers of GFR and the potential utility of cystatin C as a new marker of GFR.

2. Estimation of GFR in clinical practice**2-1. Serum creatinine**

Serum creatinine has become the most commonly used serum marker of the renal function. Serum creatinine is a metabolic product of creatine in muscle tissue. Its production rate is related to muscle mass, so that intraindividual concentrations are relatively constant. However, the serum creatinine concentration is affected by age and gender. Serum creatinine is freely filtered by the glomerulus and shows no reabsorption, but it is secreted in small amounts. An increase in the serum creatinine leads to an increase in the tubular secretion of serum creatinine, thus indicating that the serum creatinine level does not increase until the GFR has moderately decreased (about 40 ml/min/1.73 m²) (1). These findings indicate that serum creatinine is insensitive regarding the detection of small decreases in GFR, thus suggesting the existence of a so-called creatinine blind GFR area (40 – 70 ml/min/1.73 m²).

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Published online in J-STAGE: September 8, 2007

doi: 10.1254/jphs.CP0070058

2-2. Creatinine clearance

The creatinine clearance is calculated from urine creatinine, urine volume, and serum creatinine through the following equation:

$$\begin{aligned} &\text{creatinine clearance (ml/min)} \\ &= [\text{urine creatinine (mg/dl)} \times \text{urine volume (ml)}] \\ &\quad / [\text{serum creatinine (mg/dl)}] \end{aligned}$$

The creatinine clearance, which is calculated by determining its concentration in timed urine collections and simultaneously in the blood, is considered to be the gold standard endogenous method, better than determination of serum creatinine. However, creatinine is excreted via glomerular filtration and tubular secretion, which leads to an overestimation of GFR. In severely decreased GFR populations, an overestimation of GFR based on the creatinine concentration is more likely (1). In addition, the measurement of creatinine clearance requires a timed urine collection, which has proven laborious and prone to collection failure, especially in the elderly.

2-3. Prediction formulas of creatinine clearance or GFR

The prediction formulas of creatinine clearance or GFR are widely used because no effective methods for predicting GFR without a urine collection have yet been developed. The Cockcroft and Gault formula is used to estimate the creatinine clearance from the serum creatinine concentration with a correction for age, muscle mass, and sex.

Cockcroft and Gault formula (2):

$$\begin{aligned} &[\text{estimated creatinine clearance (ml/min)}] \\ &= [(140 - \text{age (y)}) \times \text{weight (kg)}^*] \\ &\quad / [72 \times \text{serum creatinine (mg/dl)}] \\ &\quad \text{*for women, } \times 0.85 \end{aligned}$$

However, this formula of GFR also leads to an overestimation in the elderly (3).

According to the guidelines of the Kidney Disease Outcomes Quality Initiative (K/DOQI), the Cockcroft and Gault formula and the formula developed from the Modification of Diet in Renal Disease Study (MDRD) is recommended for estimating GFR. The MDRD formulas were developed from 1,628 patients' data to predict GFR from age, sex, race, serum creatinine, serum albumin, and serum urea (4). However, the MDRD study population did not include an elderly population. Hence, the MDRD formula is not accurate in an elderly population (5).

MDRD formula:

$$\begin{aligned} &\text{GFR (ml/min/1.73 m}^2\text{)} \\ &= 170 \times [\text{serum creatinine (mg/dl)}]^{-0.999} \\ &\quad \times [\text{age (y)}]^{-0.176} \times [\text{serum urea (mg/dl)}]^{-0.170} \\ &\quad \times [\text{serum albumin (g/dl)}]^{0.318} \end{aligned}$$

For women, $\times 0.762$; for Japanese, $\times 0.881$ (ref. 6)

2-4. Measurement of the clearance of exogenous substances

The determination of GFR is a cumbersome procedure, ideally involving inulin infusion and urine collection under very standardized conditions. As a result, this test is performed only when precise information on the kidney function is required because it is time-consuming, labor-intensive, and expensive.

3. Cystatin C as a marker of GFR

3-1. Properties of cystatin C

Cystatin C has a low molecular weight (13 kD) and is a member of the family of cysteine protease inhibitors, which are produced by all nucleated cells. A structural analysis of the cystatin C gene and its promoter has shown this gene to be a house-keeping type, which is compatible with a stable production rate by most cells, even under inflammatory conditions (7). Because of its small size and basic pH, cystatin C is freely filtered by the glomerulus. It is not secreted, but is reabsorbed by tubular epithelial cells and subsequently catabolized so that it does not return to the blood flow (8). Because of these properties, cystatin C bears some advantages over serum creatinine. Cystatin C is independent of muscle mass, age, or sex. Most significantly, on average, GFR declines with age by approximately 1 ml/min/1.73 m²/year over the age of 40 years, and the rate of decline in GFR accelerates after 65 years of age (9). Serum creatinine alone is an unacceptable measure of renal function in the elderly. Possible reasons for this include reduced muscle mass and poor nutrition. However, serum cystatin C concentrations increase with advancing age (Fig. 1). Therefore, the measurement of cystatin C is useful, especially in the elderly (10).

The diagnostic performance of cystatin C in comparison to creatinine was analyzed in a meta-analysis on 46 studies (11). This meta-analysis suggests that cystatin C is superior to creatinine for the detection of impaired GFR in cross-sectional studies. In clinical practice, serum cystatin C has been suggested to optimize the early detection of diabetic (12) or hypertensive nephropathy (13).

3-2. Formulas using the serum cystatin C concentration to estimate GFR

Some formulas using the serum cystatin C concentration based on the particle-enhanced immunonephelometric assay (PENIA) or immunoturbidimetric assay (PETIA) in order to estimate GFR have recently been reported (Table 1) (14–19). The diagnostic accuracy of three cystatin C-based formulas (Larson, Hoek, and Filler formulae) that used an immunonephelometric

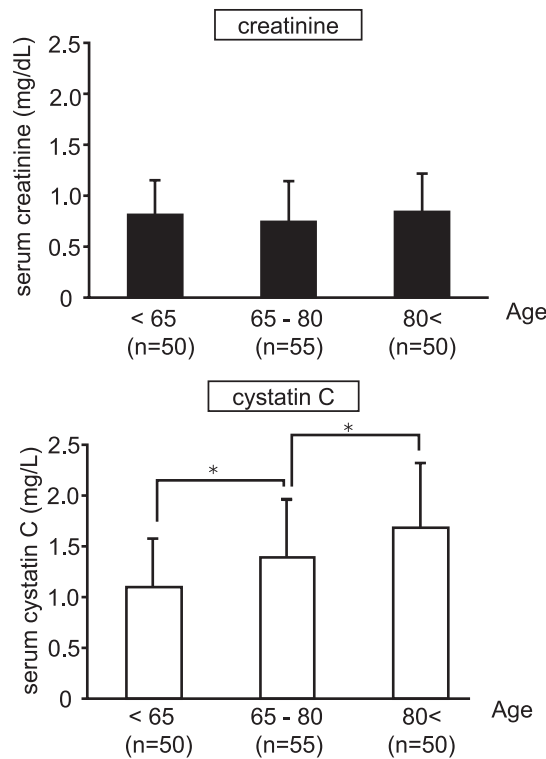


Fig. 1. A comparison of the serum creatinine and cystatin C concentrations according to age brackets. Each column represents the mean serum concentration of creatinine or cystatin C with S.D. Data were analyzed by one-way analysis of variance (ANOVA) followed by Tukey's test. * $P < 0.01$, in comparison to age 65 – 80.

method was evaluated in liver transplant recipients (20) and in kidney transplant recipients (21). In both reports, the Hoek formula showed the best overall performance for GFR with respect to bias, precision, and

accuracy. However, these cystatin C-based formulas were generated and validated in smaller samples in a single center study. Future studies need to evaluate formulas for GFR estimates based on cystatin C in large, diverse populations.

3-3. Factors altering the serum cystatin C concentration

It is important to confirm whether the cystatin C production is constant. To our knowledge, only a few circumstances have been identified that have an impact on the serum cystatin C concentration. Large doses of glucocorticoids have been shown to increase the serum cystatin C concentration (22, 23). In contrast, low or medium doses of glucocorticoids do not seem to alter the serum cystatin C concentration (24). On the other hand, hypothyroidism and hyperthyroidism have been reported to alter the serum cystatin C concentration (25), and thyroid function may be considered when cystatin C is used as a marker of renal function.

4. The clinical utility of the serum cystatin C with regard to drug dose adjustment

Prediction formulas of creatinine clearance or GFR are widely used, but these formulas of GFR often lead to an overestimation in the elderly (3, 5). The dose of drugs eliminated by the kidney must be adjusted according to the degree of decrease in GFR, especially when narrow therapeutic range drugs, such as glycopeptide antibiotics, aminoglycoside antibiotics, and digoxin, are involved. In clinical practice, these drugs are often used in the elderly. However, previous studies have shown that physicians routinely overestimate the renal function

Table 1. Formulas using the serum cystatin C concentration to estimate GFR

Based on the immunonephelometric method

Filler's formula (14):

$$\log(\text{GFR}) (\text{ml/min}/1.73 \text{ m}^2) = 1.962 + [1.123 \times \log(1 / \text{serum cystatin C (mg/L)})]$$

Hoek's formula (15):

$$\text{GFR} (\text{ml/min}/1.73 \text{ m}^2) = -4.32 + 80.35 / \text{serum cystatin C}$$

Larsson's formula (16):

$$\text{GFR} (\text{ml/min}) = 77.24 \times (\text{serum cystatin C})^{-1.2623}$$

Based on the immunoturbidimetric method

Grubb's formula 1 (17):

$$\text{GFR} (\text{ml/min}/1.73 \text{ m}^2) = 86.49 \times (\text{serum cystatin C})^{-1.686}$$

For women, a correction factor of 0.948 was used.

Sjöström's formula (18):

$$\text{GFR} (\text{ml/min}/1.73 \text{ m}^2) = 124 / \text{serum cystatin C} - 22.3$$

Grubb's formula 2 (19):

$$\text{GFR} (\text{ml/min}) = 99.19 \times (\text{serum cystatin C})^{-1.713}$$

For women, a correction factor of 0.823 was used.

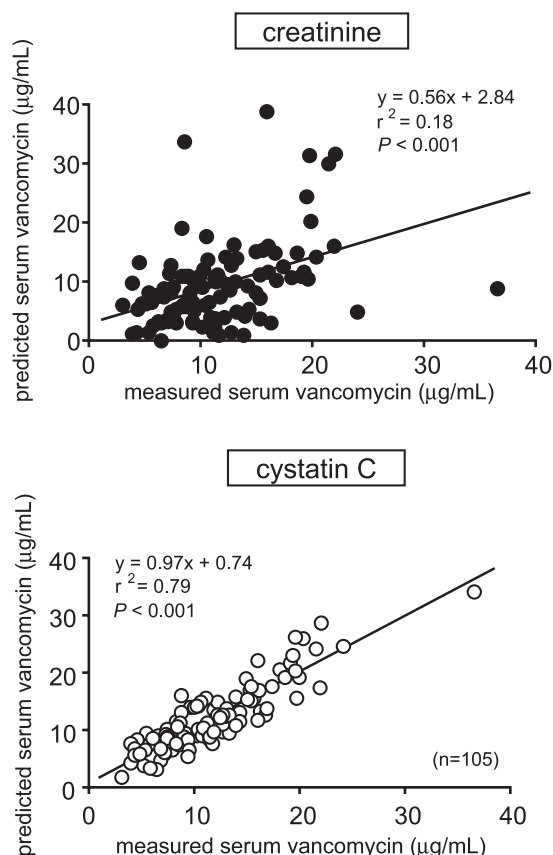


Fig. 2. Correlations between the measured and predicted vancomycin concentrations by creatinine and cystatin C. A slight, but significant, correlation was seen between the measured and predicted vancomycin concentrations using the serum creatinine concentration ($r^2 = 0.18$, $P < 0.001$), and a remarkable correlation was also observed between the measured and predicted vancomycin concentrations using the serum cystatin C concentration ($r^2 = 0.79$, $P < 0.001$).

when using the serum creatinine concentration as a marker of renal function in the elderly (26). This may cause the prescribing physician to treat such patients with unnecessarily high drug doses, thus increasing the cost and possibly resulting in side effects. Therefore, cystatin C may be more appropriate for adjusting the dose of drugs that are mainly eliminated by the kidney. Hermida et al. (27) reported that cystatin C seems to be a valid alternative as a GFR marker with regard to drug dose adjustment for amikacin and vancomycin, which are excreted via glomerular filtration, in patients with hepatic dysfunction. We previously reported the predictive performance of the serum vancomycin concentrations, based on the use of the serum cystatin C concentration, to be better than those based on the serum creatinine concentration, especially for an elderly population (Fig. 2). Therefore, determining the cystatin C concentration may be more appropriate for establishing the appropriate dose adjustment of drugs that are mainly

eliminated by the kidney (9).

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