The Search Continues—An Ideal Marker of GFR

The glomerular filtration rate (GFR) is generally considered the best measure of renal function despite the fact that the kidney performs an array of duties, including salt and water balance, erythropoiesis, bone metabolism, electrolyte homeostasis, and blood pressure control. GFR is traditionally measured as the renal clearance of a particular substance from plasma and is expressed as the volume of plasma that can be completely cleared of that substance in a unit of time. The ideal marker for GFR determinations would appear endogenously in the plasma at a constant rate, be freely filtered at the glomerulus, be neither reabsorbed nor secreted by the renal tubule, and undergo no extrarenal elimination. Although the ideal marker for measuring GFR has yet to be found, these characteristics can be useful benchmarks for comparing the advantages and disadvantages of new methods for GFR quantification.

Measurement of urea marked the beginning of efforts to quantify renal function with its isolation by Rouelle in 1773 *[1]*. Subsequently, Strauss introduced blood urea as a diagnostic test for renal disease in 1903. The concept of clearance as a measure of renal function followed in 1929 *[2]* and was subsequently extended to creatinine in the early 1930s *[1]*.

Blood urea nitrogen (BUN) concentration is generally recognized to be a poor measure of renal function, in that it possesses few of the attributes of an ideal marker of GFR. It is produced at variable rates, is affected by a number of disease states (congestive heart failure, malnutrition, hyperalimentation), and undergoes renal tubular reabsorption.

Serum creatinine determination has become a mainstay in the standard laboratory profile of renal function because of its convenience and low cost. Nevertheless, serum creatinine remains a crude marker of GFR. Creatinine concentrations are insensitive to detection of mild to moderate reductions in GFR. This is due to the nonlinear relation between concentrations of creatinine in the blood and GFR. For example, a change in serum creatinine from 53 μmol/L (0.6 mg/dL) to 106 μmol/L (1.2 mg/dL) reflects ~50% decline in GFR despite the latter value falling within the normal range. If a previous baseline value for serum creatinine did not exist for comparison, a value of 106 (1.2) would not draw clinical attention to a potential reduction in GFR. Nephrologists are often consulted as an emergency when a patient's creatinine rises from 442 μmol/L (5 mg/dL) to 619 μmol/L (7 mg/dL), which may be far less critical in that GFR has fallen from ~20 mL/min to 15 mL/min. Creatinine is a metabolic product of creatine and phosphocreatine found in muscle and, as such, reflects muscle mass and varies little from day to day *[3]*. However, age- and gender-associated differences in creatinine production are proportional to muscle mass, and creatinine generation can vary significantly in a given individual over time when muscle mass changes *[4, 5]*. Creatinine is small, circulates unbound to plasma proteins, and is freely filtered at the glomerulus but undergoes tubular secretion into the urinary space *[6]*. Tubular secretion of creatinine is not constant and varies, not only within an individual, but between individuals. Further, the proportion of total renal creatinine excretion due to tubular secretion increases with decreasing renal function. This could lead to further amplification of the overestimation of GFR, which creatinine clearance represents *[7]*. Several substances can interfere with laboratory measurements of creatinine. Glucose, uric acid, ketones, plasma proteins, and cephalosporins may lead to falsely high creatinine values when the Jaffe colorimetric method is used *[8, 9]*. 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.

Clearance of various radionuclide markers, including ^{99m}Tc-labeled diethylenetriaminepentaacetic acid (DTPA), ^{51}Cr-labeled EDTA, and ^{125}I-labeled iothalamate, have been used as reliable measures of glomerular filtration but are costly, involve special specimen handling, and require radiation exposure.

Thus, a method to quantify GFR that is accurate, efficient, and safe continues to elude clinicians. In recent years, O'Reilly et al. reported that the plasma "decay" or disappearance of iohexol represented a new method of measuring GFR *[10]*. Later reports proposed that iohexol clearance replace inulin clearance as the new "gold standard" of GFR determinants, and numerous investigators have reported similar results with iohexol *[11–14]*. Additionally, my colleagues and I reported that plasma iohexol clearance was a safe, accurate, and efficient way to measure residual renal function in hemodialysis patients to better tailor their dialysis prescription *[15]*. Drawbacks to iohexol-derived GFR include the need for a blood draw 4 to 6 h after iohexol administration and a history of iodine allergy precluding its use.

In 1985, Simonsen et al. reported that the reciprocal of serum concentrations of cystatin C correlated closely with ^{51}Cr-labeled EDTA-derived GFR determinations *[16]*. A number of subsequent reports have confirmed that cystatin C is an accurate marker of GFR *[17, 18]*. A small protein derived from the cystatin superfamily of cysteine protease inhibitors *[19]*, cystatin C is produced by all nucleated cells and its production rate is unaltered in inflammatory conditions; glomerular filtration removes cystatin C from the circulation. Thus, cystatin C meets many of the criteria of an ideal GFR marker. Early methods of cystatin C quantification (enzyme-amplified single radial immunodiffusion), however, were slow, impractical for single sample analysis, and did not allow automation. In this issue of *Clinical Chemistry*, Finney et al. *[20]* describe a new particle-enhanced immunonephelometry method for cystatin C determinations, and Filler et al.

[21] report that cystatin C may represent a better marker of GFR than creatinine when measured by a particle-enhanced turbidimetric assay. The advantages of cystatin C include its endogenous nature, thus obviating the need for administration of an exogenous marker such as iohexol. Similarly, the risk of allergic reaction would not exist with cystatin C.

The rapid development of therapeutic interventions involving transplantation, antimicrobial therapy, oncology, and intensive care medicine has generated an increasing demand for fast, accurate, and simple methods for GFR determinations. In theory, cystatin C measurements in plasma represent a valuable contribution to diagnostic practices, but further clinical experience with this methodology will be necessary before its role in clinical practice can be validated.

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