Challenges in Measuring Glomerular Filtration Rate: A Clinical Laboratory Perspective

Jesse C. Seegmiller, John H. Eckfeldt, and John C. Lieske

The assessment of kidney function is a cornerstone in the clinical management and health of the patient. Although the kidneys perform many physiologic functions and are essential for maintaining homeostasis, kidney function is typically evaluated, quantitated, and understood using the glomerular filtration rate (GFR). Although GFR can be directly measured using a variety of externally administered glomerular filtration markers, in general practice, the GFR is usually estimated (eGFR) using endogenous markers that are cleared primarily by kidney filtration. Common situations exist where the GFR needs to be measured (mGFR) in order to proceed with care. This manuscript will review laboratory challenges in the assessment of GFR. Key points to consider when implementing a mGFR testing protocol are the following: marker selection, clearance methodology (urinary vs solely plasma measurements of filtration marker), sample collection, number of samples to collect, staff required, and analytical measurement technology for the filtration marker selected. We suggest those wanting to implement mGFR testing examine site-specific institutional resources along with patient population and proceed with the approaches best suited for their clinical needs and laboratory resources available.

Key Words: Glomerular filtration rate, Creatinine, Cystatin C, Iothalamate, Iohexol

INTRODUCTION

The kidney performs many key physiological functions, and a minimum level of kidney function is essential for life. However, glomerular filtration rate (GFR) is typically considered the parameter that best reflects overall kidney health and kidney function.[1] Therefore, a practical way to accurately assess a patient's GFR is required by physicians. GFR is often also a key outcome parameter in clinical trials. In all of these settings, it is important to balance cost and practicality with accuracy of the measured glomerular filtration rate (mGFR) protocol employed. This paper will focus on current measurement procedures commonly used to measure GFR, focusing on strengths and weaknesses of each.

GENERAL OVERVIEW OF GFR MEASUREMENT

An ideal marker of GFR must possess all of the following characteristics in order to accurately represent true GFR: (1) its sole route of elimination must be through the kidney via glomerular filtration, (2) the marker must be freely filtered by the glomerulus (eg, not subject to protein binding), (3) there is no elimination via tubular secretion, and (4) the marker is not reabsorbed after being filtered by the glomerulus. When all these conditions are met, kidney clearance of the marker would equal the GFR.[2] GFR markers can either be endogenously produced or exogenously administered for the sole purpose of measuring their elimination. If the rate of production of an endogenous marker is constant and GFR is in steady state (ie, not changing rapidly), then the blood concentration of this marker will be inversely proportional to GFR. All filtration markers should be easy to measure analytically. When examining either endogenous or exogenous filtration markers, the GFR must be calculated in one of two manners. (1) for a kidney clearance study, the blood concentration is monitored during a timed urine collection and the amount of the filtration marker excreted in the urine is measured. Then, GFR is calculated based upon the kidney elimination of the marker and the blood concentration during the collection. (2) For a plasma disappearance study, the exogenous marker is administered as a single bolus. Blood is sampled multiple times after that to reconstruct a curve based on its elimination from the blood stream. The rate of elimination will then equal GFR. Details of both endogenous and exogenous filtration marker measurement procedures follow. Often GFR measurements are indexed to body surface area. However, the appropriateness of indexing GFR to body surface area may depend on the clinical presentation or situation.[3,4] In particular, this may be misleading in very large, small, or obese patients. Thus, both the total GFR and GFR indexed to body surface area are often reported to allow clinical interpretation in a specific patient.

When interpreting GFR comparison studies, it is important to understand that precision, which is simply the repeatability of the measurements, is not the same as accuracy, which is closeness of the measured result to the true GFR value (ie, "trueness"). Note that in current metrological terminology, "accuracy" encompasses both "precision" and "trueness" because without good "precision," a measurement procedure cannot consistently provide results close to the true value. These distinctions

From the Department of Laboratory Medicine and Pathology, University of Minnesota, Minneapolis, MN; Department of Laboratory Medicine and Pathology; and Division of Nephrology and Hypertension, Mayo Clinic, Rochester, MN.

Support: J.C.S. and J.H.E. have received research funds for cystatin C standardization and Beta-trace protein evaluation from Siemens Corporation.

Financial Disclosure: J.H.E. has performed consulting services for the Gentian Corporation. J.C.L. has a research project on Beta-trace protein with Siemens and past research grant for cystatin C work from Gentian Corporation.

Address correspondence to Jesse C. Seegmiller, PhD, DABCC, Department of Laboratory Medicine and Pathology, University of Minnesota, 420 Delaware St SE - MMC 609, Minneapolis, MN 55455 USA. E-mail: jseegmil@umn.edu

1548-5595/$36.00

https://doi.org/10.1053/j.ackd.2017.10.006

are highlighted during comparison studies since results from various measurement procedures that use different markers may be highly correlated, yet may not have comparable "accuracy" due to biases of one (or both) of the measurement procedures being compared.

ENDOGENOUS MARKERS

Creatinine

Creatinine is by far the most common serum marker used to assess GFR in clinical practice. Nevertheless, it is recognized that creatinine is imperfect for this purpose. One reason for the nonideal GFR behavior of creatinine is tubular secretion, which has been demonstrated by comparing kidney clearance of creatinine and the "gold standard" GFR marker inulin.[5] The level of creatinine eliminated by secretion appears to increase as GFR declines, making creatinine clearance a particularly poor marker in individuals with low GFR.[6,7] Another unfortunate attribute of creatinine is that its metabolic formation may not be constant and can also vary among individuals.[8] Fortunately, skeletal muscle mass, which is the major source of endogenous creatinine production, correlates with certain demographic features including age, sex, body size, and race. Thus, equations have been developed that can estimate GFR from serum creatinine by using these demographic factors.[9] Examples are the Cockcroft-Gault formula,[10] the modification of diet in renal disease equation,[11] and Chronic Kidney Disease Epidemiology Collaboration equation.[12] It should be understood that the Cockcroft-Gault formula was designed to estimate creatinine clearance and the equation does not yield results indexed to a standard body size, while the modification of diet in kidney disease and Chronic Kidney Disease Epidemiology Collaboration equations were statistically developed to estimate GFR and are indexed to 1.73 m^2 of body surface area.

These equations perform reasonably well in many clinical situations to estimate the GFR. However, the scatter and uncertainty in an estimated glomerular filtration rate (eGFR) value with respect to the true GFR in any given patient is still a potential confounder.[13] These concerns are amplified in any individual with muscle mass not typical for their age and sex. Examples include patients who are malnourished, very fit athletes, or patient's status after limb amputation. Diet is also a consideration because creatine in meats is converted with cooking to creatinine, and thus, large meals containing meat can significantly raise the serum creatinine and make a creatinine-based eGFR falsely low. In some cases, it is critically important to have a very precise and accurate idea of a patient's true GFR. Examples would include patients being considered for living kidney donation or that are being dosed with nephrotoxic chemotherapy agents and in other situations where the patient's GFR is changing over hours to days (where the serum endogenous marker can significantly lag the GFR change) yet an accurate GFR is needed clinically. In such circumstances, direct measurement of GFR is reasonable despite the added time, effort, and expense required.

Another potential issue with serum creatinine–based eGFR values, now largely overcome, relates to standardization of the serum creatinine measurement itself.[14] Due to the combined efforts of laboratorians, traceable calibration to isotope-dilution mass spectrometry reference measurement procedures and reference materials have now been implemented among the vast majority of commercially available clinical creatinine measurement procedures. While calibration standardization is helpful in harmonizing interlaboratory eGFR values, calibration alone cannot account for potential analytical interferences that can affect the major methodologies.[14] Although the newer enzymatic assays are in general less subject to interference, they do not completely eliminate this problem. Indeed, in some circumstances, a Jaffe-based measurement procedure may provide more accurate creatinine concentrations.[15] A report of before and after calibration standardization elegantly demonstrated that even after standardization methodology biases can persist,[16] and measurement procedure calibration does not solve all the problem of analytical biases in serum creatinine measurements due to physiological or dietary factors discussed in the previous paragraph.[17]

CLINICAL SUMMARY

- GFR is a key physiologic parameter for patient care.
- It is important to consider the choice of any endogenous GFR marker in light of patient specific factors that can potentially confound them.
- Endogenous markers are widely used to estimate GFR, but in certain patient circumstances it may be necessary to directly measure GFR using exogenous markers that are cleared by glomerular filtration.
- In depth knowledge of clearance methodologies, timing and methods of sample collection, and patient-specific limitations associated with each approach is imperative.

Despite all of these considerations and caveats, serum creatinine remains the workhorse of eGFR determination in routine clinical medicine today and will likely remain so for the foreseeable future. Thus, the major challenge for clinicians and laboratorians is to recognize the potential confounders of serum creatinine and when alternative measurement procedures might be used to better assess GFR. College of American Pathology (CAP) and most all larger clinical laboratory proficiency testing programs are readily available for creatinine in both urine and serum.[18] Commercially available automated analyzers have existed for many decades to analyze serum, plasma, and urine specimens.

Cystatin C

Cystatin C, a small (~13 kDa) molecular weight protein, is also an endogenous marker useful for eGFR determinations. Cystatin C is freely filtered by the glomerulus and,