HHS Public Access

Author manuscript

Clin Chem. Author manuscript; available in PMC 2016 December 04.

Published in final edited form as:

Clin Chem. 2012 April ; 58(4): 680–689. doi:10.1373/clinchem.2011.167494.

Established and Emerging Markers of Kidney Function

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Abstract

BACKGROUND—The kidney performs a multitude of essential functions to maintain homeostasis. In clinical medicine, glomerular filtration rate (GFR) provides the best index of overall kidney function, and protein-uria adds additional information on renal and nonrenal prognosis. Several novel biomarkers of kidney injury and function are under investigation.

CONTENT—Plasma creatinine concentration is the most widely used measure for estimation of GFR. Plasma cystatin C and β-trace protein may eventually prove to be superior to creatinine. GFR may be measured directly by use of exogenous filtration markers, although their role is primarily limited to the research setting. Real-time, noninvasive measurement of GFR by using fluorescently labeled markers may be available in the future. Novel biomarkers of tubular injury such as neutrophil gelatinase-associated lipocalin, kidney injury molecule-1, liver-type fatty acid binding protein, N-acetyl-β-(D)-glucosaminidase, and interleukin-18 may enable the early detection of acute kidney injury before or in the absence of a change in GFR.

SUMMARY—A variety of methods are available to assist clinicians in the assessment of kidney function and injury. Ongoing investigation will help determine the utility of several new markers and clarify their role in the care of patients with and at risk for kidney disease.

The kidney performs many excretory and regulatory functions necessary to sustain life. Under normal conditions, the kidney not only functions to maintain the constancy of the extracellular environment by excretion of the waste products of metabolism and the adjustment of urinary water and electrolyte excretion, but also is intricately involved in the regulation of blood pressure, red blood cell production, and bone mineral metabolism. With this in mind, it is not surprising that a variety of diverse biological markers are employed in clinical practice to monitor the physiologic status of the kidney. Many of the markers in use presently have been employed for decades, although there has been a surge in biomarker discovery in recent years that promises to augment assessment of kidney function and injury.

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Author Contributions: All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.

Authors' Disclosures or Potential Conflicts of Interest: No authors declared any potential conflicts of interest.

Estimated glomerular filtration rate (eGFR)[3] is the most important variable in the assessment of patients with suspected or known kidney disease. eGFR is typically reported in milliliters per minute and corrected for standard body surface area [$mL \cdot min^{-1} \cdot (1.73\ m^2)^{-1}$]. Sustained or chronically decreased GFR is generally accompanied by associated diminution of other renal functional parameters, resulting in altered electrolyte and volume balance, decreased red blood cell production, hypertension, and/or altered bone mineral metabolism. As a result, eGFR is generally accepted as the best measure of overall kidney function. Accurate estimation of GFR allows for appropriate prognostication and monitoring over time of patients with chronic kidney disease (CKD). The National Kidney Foundation Kidney Disease and Quality Initiative has defined stages of CKD largely on the basis of the level of eGFR (see Table 1) (1). In addition, 2 proposals have been developed for the classification of acute kidney injury (AKI), the Acute Kidney Injury Network (AKIN) and RIFLE (risk, injury, failure, loss, end-stage renal disease) criteria (1, 2), which are based on fall in GFR as inferred by changes in creatinine or urine output (see Tables 2 and 3). Several markers of GFR may be assessed with routine blood testing. In addition, endogenous and exogenous markers may be measured by using clearance-based methods. Novel urinary markers of kidney injury may complement assessment of GFR and appear to be predictive of the development of AKI and CKD.

Serum or Plasma Markers of Kidney Function

Historically, urea was the first marker used to formally assess kidney function. Urea is the major form of nitrogenous waste in the body. It is the product of protein and amino acid metabolism and eliminated almost entirely via urinary excretion. Although originally discovered decades earlier, in 1827 Richard Bright was the first to associate an accumulation of urea in the blood with its decrease in the urine among individuals with diseased kidneys (3). Blood urea nitrogen (BUN) quantification was eventually introduced into clinical medicine as a diagnostic test in the early 1900s (3). Although assessment of BUN remains a widely used metric to assess kidney function, it is now generally understood to be a suboptimal marker for this purpose. Increased concentrations of BUN may be observed in a number of settings that are not directly related to alterations in GFR. For example, urea is readily reabsorbed by the tubules, particularly during volume depletion, resulting in increased plasma concentrations while GFR is preserved. In addition, increased BUN concentrations may be seen with increased dietary protein intake, hypercatabolism, corticosteroid use, or gastrointestinal bleeding. Therefore, interpretation of BUN concentrations needs to be carefully considered in the clinical context.

Serum creatinine supplanted BUN for the assessment of kidney function in the mid-1900s and remains the most widely used laboratory test to estimate GFR. Creatinine is formed at a relatively constant rate as a result of the nonenzymatic dehydration of muscle creatine and is therefore roughly proportional to muscle mass. Creatinine is freely filtered by the glomerulus and is not reabsorbed by the renal tubules; however, it is secreted at variable

[3]Nonstandard abbreviations: eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; AKI, acute kidney injury; BUN, blood urea nitrogen; MDRD, modification of diet in renal disease; NKDEP, National Kidney Disease Education Program; BTP, β-trace protein; DTPA, diethylenetriamine penta-acetic acid.

rates. Drugs such as cimetidine and trimethoprim inhibit tubular secretion of creatinine. More problematic is the fact that tubular secretion of creatinine is increased proportionally relative to its glomerular filtration as kidney function declines, resulting in a significant overestimation of true GFR. As a result, an increase in serum creatinine may not be observed until a substantial decrease in GFR has occurred. Additional limitations to the use of serum creatinine to estimate GFR arise from the substantial variability in between-person and within-person creatinine generation. In an attempt to account for this variation, several serum creatinine–based equations have been developed to estimate GFR, the most notable being the Cockcroft–Gault, Modification of Diet in Renal Disease (MDRD), and CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equations for adults and the Schwartz equation for children. Although these equations generally increase the reliability of estimating the GFR, they all have limitations. For example, the MDRD equation is known to underestimate the GFR, particularly at lower creatinine concentrations, whereas the Cockcroft–Gault and Schwartz equations have been shown to overestimate the GFR, especially at lower creatinine concentrations. Lastly, the equations do not account for differences that may occur as a result of unusually high or low muscle mass, extreme diets (vegan or excessive meat consumption), or ethnic variation of groups not included in their derivation.

Historically, considerable variability existed with respect to serum creatinine measurement, generally resulting in less accurate estimation of GFR when serum creatinine concentrations were within or slightly above the reference interval (4). In 2008, the National Kidney Disease Education Program (NKDEP) in collaboration with the IFCC and the European Communities Confederation of Clinical Chemistry launched the Creatinine Standardization Program to reduce interlaboratory variability in creatinine assay calibration (5). Today, most laboratories now use a creatinine assay that has calibration traceable to an isotope dilution mass spectroscopy method, enabling interlaboratory comparisons (4). Equations for estimating GFR using creatinine are provided in Table 4 (6–10). The reader is referred to the NKDEP website for guidance regarding proper use of GFR estimating equations (5).

LOW MOLECULAR WEIGHT PROTEINS AS GFR MARKERS

Measured concentrations of several low molecular weight proteins, including β_2-microglobulin, cystatin C, and β-trace protein (BTP), have been evaluated as potential markers of GFR. In general, these proteins are freely filtered by the glomerulus, reabsorbed and catabolized, but not secreted by the renal tubules. As a result, reductions in GFR are associated with increased plasma concentrations.

β_2-Microglobulin is an 11.8-kDa protein that is the light chain of the MHC I molecule expressed on the cell surface of all nucleated cells. It dissociates from the heavy chain in the setting of cellular turnover and enters the circulation as a monomer. β_2-Microglobulin is filtered at the glomerulus and almost entirely reabsorbed and catabolized by proximal tubular cells (11). Unlike creatinine, serum concentrations appear to be largely independent of age and muscle mass (12); however, there does not appear to be a clear advantage of β_2-microglobulin over serum creatinine in detecting small changes in GFR (13). A major factor limiting the utility of β_2-microglobulin as a marker of renal function is its nonspecificity,

because serum β_2-microglobulin concentrations are known to increase in several malignancies and inflammatory states (12, 14).

Serum cystatin C has generated considerable enthusiasm in recent years as a marker of GFR. Cystatin C is a 122 amino acid low molecular weight protein that is a member of the cysteine proteinase inhibitors (15). It is produced at a constant rate by all nucleated cells and is freely filtered by the glomerulus, reabsorbed and catabolized, but not secreted by the renal tubules (15). Unlike creatinine, serum cystatin C concentration appears to be independent of age, sex, and muscle mass(16). Cystatin C may be more reliable than serum creatinine–based methods in estimating GFR, particularly in those individuals with a mild reduction in GFR, in whom changes in serum creatinine are typically not observed (the so-called creatinine blind range of GFR) (17). Cystatin C may also be superior to creatinine in estimation of mortality and cardiovascular outcomes (18). Cystatin C has been reported to rise faster than creatinine after a fall in GFR, enabling earlier identification of AKI (19, 20). Several cystatin C–based equations to estimate GFR appear to be simpler and more accurate than creatinine-based equations (21). More recently, equations have been derived that incorporate serum cystatin C and creatinine and appear to outperform those using either of these 2 markers alone (22–24). Circulating cystatin C concentrations may be affected by corticosteroid administration and thyroid dysfunction (25). In addition, it should be noted that there are ongoing concerns related to the lack of standardization in cystatin C measurement. White et al. (26) recently found that there were significant differences in cystatin C measurement between laboratories even when the same assay was used from the same manufacturer. The IFCC Working Group for Standardization of Cystatin C is working to remedy these issues and in collaboration with the Institute for Reference Materials and Measurements has produced and characterized a cystatin C reference material (ERM-DA471/IFCC) (27).

More recently, serum BTP has been investigated as a marker of GFR. BTP (also known as prostaglandin D2 synthase) is a low molecular weight protein that is generated at a constant rate by glial cells in the central nervous system (28). It is freely filtered by the glomerulus and reabsorbed by the proximal tubule with minimal nonrenal elimination (29). Recent studies suggest that serum BTP concentrations perform at a similar level to creatinine and cystatin C not only in the estimation of GFR, but also in the prediction of progressive renal dysfunction (30). Equations to estimate GFR have been derived with the use of BTP (31, 32), although further validation is necessary in diverse populations. Like cystatin-C, corticosteroid administration appears to impact serum concentrations of BTP (33). Additional work is needed to confirm the utility of BTP in the routine assessment of GFR and to establish reference laboratory standards to ensure inter- and intralaboratory consistency in measurement.

As a whole, serum markers appear to provide adequate assessment of GFR in most clinical situations. There are many advantages to their utilization, primarily related to low technical demand of testing as well as demonstrated ability (serum creatinine and BUN) and potential (cystatin C and BTP) to provide rapid assessment. For research settings, or clinical circumstances in which estimation of GFR by serum markers is likely to be inaccurate or when precise GFR measurements are required for clinical decision-making (e.g., clearance

for kidney donation in an individual with borderline eGFR), clearance-based techniques can be used to provide a more accurate estimation of true GFR.

Clearance-Based Markers of Kidney Function

Using the concepts of renal clearance, one may accurately estimate the GFR using endogenous or exogenous substances. The renal clearance of a specific substance is understood to be the volume of plasma that can be completely cleared of that substance in a unit of time (34). This is expressed as:

$$C_x = \frac{U_x \times V}{P_x}$$

where C is the clearance of a substance x, U is the urinary concentration of substance x, V is the urine flow rate, and P is the plasma concentration of substance x. Homer Smith is widely credited with introducing renal clearance methodologies and popularizing their utility in the noninvasive measurement of GFR. In his seminal text *The Kidney: Structure and Function in Health and Disease* (3), Homer Smith described properties of a substance suitable for the clearance-based estimation of GFR, in that it must:

1. Be completely filterable at the glomerulus.
2. Not be synthesized or destroyed by the tubules.
3. Not be reabsorbed or excreted by the tubules.
4. Be physiologically inert, so that its administration does not have any disturbing effect upon the body.

In addition to those specifications outlined by Smith, an ideal substance should also be unbound to plasma proteins, not undergo extrarenal elimination, and be easy and inexpensive to measure.

Inulin, a polymer of fructose found in tubers, is an exogenous substance that fulfills the criteria outlined above. The classic method for using inulin clearance to measure GFR described by Homer Smith requires early morning testing in a fasting state, oral fluid loading to promote diuresis, bladder catheterization to ensure complete urine collection, continuous inulin infusion at a constant rate, and multiple urine and blood collections once a steady state has been achieved (3). Inulin clearance is then calculated from the plasma concentration, urine concentration, and urine flow rate. Inulin clearance is still regarded as the gold standard for the measurement of GFR, although it is rarely used clinically because of the restricted availability of inulin and invasiveness of the procedure. Currently, inulin measurement is not offered in most clinical laboratories. Therefore, clearance-based protocols that use other markers are currently employed when measured GFR is desired.

Timed urine collections may be performed to estimate creatinine clearance, which is an approximation of GFR. Typically, a 24-h urine collection is performed with a single blood draw shortly before or after the collection to measure serum creatinine. Shorter timed collections may be appropriate for hospitalized individuals with rapidly changing renal

function (35). Although timed urine collection is relatively easy to perform, there are a number of practical issues that limit its use for creatinine clearance measurement and interpretation. As described above, creatinine clearance systematically overestimates true GFR because of tubular secretion of creatinine, particularly when the GFR is decreased. Because urea is reabsorbed but not secreted, whereas creatinine is secreted but not reabosorbed, the true GFR lies between the measured urea clearance and the creatinine clearance, suggesting a possible role for simultaneous assessment of creatinine and urea clearance (10). The major concern with 24-h urine collections from outpatients is the possibility of over- or undercollections, which substantially limits their reliability.

Plasma clearance methods may be employed in the assessment of GFR. Testing typically involves the injection of an exogenous marker in a single bolus dose and measuring the plasma disappearance of the marker by using serial blood draws over a period of several hours. These methods obviate the need for a urine collection and are typically completed in a shorter period of time than conventional timed urine creatinine clearance measurement. Markers currently in use include a number of radioactive [^{99m}Tc–diethylenetriamine pentaacetic acid (DTPA), ^{51}Cr-EDTA, ^{125}I-iothalamate] and nonradioactive (iohexol and iothalamate) substances. Single-injection methods to measure plasma clearance of each of these markers have been validated against urinary clearance of inulin (36, 37) for the measurement of GFR. Radionuclide markers have the advantage of ease of measurement, which must be balanced against the disadvantage of radiation exposure and the requirement for facilities to appropriately store and dispose of radioactive materials. The use of unlabeled iothalamate and iohexol eliminate the issues related to radiation (36). Single blood-sampling procedures and abbreviated study periods have been evaluated for plasma clearance markers, although bias and imprecision may be concerns in patients with CKD (38, 39).

Novel Methods for GFR Estimation

An ideal functional marker in the setting of AKI is one that permits real-time point-of-care measurement of GFR. Although no such marker currently exists for clinical care, separate groups have reported promising results using fluorescent markers in preclinical models. Rabito et al. (40) described a novel optical approach for GFR determination using a fluorescent GFR marker, carbostyril124–DTPA–europium, with the same clearance characteristics as ^{125}I-iothalamate. Following a single intravenous injection of marker into rats, continuous real-time monitoring of clearance was possible by use of transcutaneous fluorescence measurements. More recently, Schock-Kusch et al. (41) investigated FITC-labeled sinistrin, the active pharmaceutical ingredient of the commercially available GFR marker Inutest, as a marker of GFR. In freely moving rats, real-time monitoring of FITC-sinistrin elimination kinetics was performed by use of a portable transcutaneous device. Clearance measurements that use this method were comparable to those obtained by using a typical plasma clearance technique in healthy rats and rats with kidney disease. Wang et al. (42) used fluorescent conjugates of inulin (filtered marker) and dextran (nonfiltered marker) and a portable optical ratiometric fluorescence analyzer to estimate GFR in dogs and pigs. GFR determination 60 min after a bolus infusion of the markers was comparable to that performed by use of standard 6-h iohexol plasma clearance methods. These developments

have generated considerable enthusiasm because they indicate that real-time monitoring of GFR is attainable, and validation in the clinical setting is highly anticipated.

Beyond GFR—The Importance of Albuminuria

Despite the high concentration of albumin in the plasma, only small amounts of albumin normally appear in the urine owing to size and charge selectivity of the glomerular filtration barrier along with tubular re-absorption of filtered albumin. Albuminuria has been known to physicians since the 1800s, most notably through Richard Bright's observations on dropsy, an ancient term referring to generalized edema that we now know may arise from heart failure, liver disease, or the nephrotic syndrome. Quantification of proteinuria (the majority of which is usually albumin) is now a central part of screening for and monitoring of kidney disease. Dividing the urine albumin or protein concentration by the urine creatinine concentration provides an estimate, in grams, of 24-h urinary albumin excretion; this method implicitly assumes constant 1 g/24 h of creatinine excretion, and may be inappropriate in those with rapidly changing GFR or large variations in creatinine generation rate (43). Albuminuria is one of the most prognostically significant biomarkers of kidney disease outcomes and even cardiovascular disease and death (44). Across every stratum of eGFR, higher amounts of proteinuria or albuminuria signal an increased risk of death, cardiovascular disease, and kidney disease progression. Albuminuria has been proposed as an additional biomarker to classify stages of CKD in view of its additional clinical predictive ability above and beyond eGFR (45). The pathophysiologic correlates of albuminuria are variable: in those patients with conditions such as nephrotic syndrome, diffuse effacement of podocyte foot processes with loss of glomerular permselectivity is the cause of albuminuria. Smaller amounts of albuminuria may accompany generalized endothelial dysfunction and serve as a window into systemic small vessel disease. In other patients, albuminuria may be a consequence of proximal tubular dysfunction and loss of tubular reabsorptive capacity. The FDA has qualified albuminuria as a preclinical (i.e., in animal studies) biomarker of nephrotoxic tubular injury on the basis of carefully conducted rodent studies involving a range of nephrotoxins (46). Albuminuria is higher in those who go on to develop AKI and may serve as an additional tool for renal risk stratification (47). In patients with established proteinuric kidney disease, albuminuria reduction is often used as a surrogate target in clinical practice, although supporting data are lacking to make definitive clinical recommendations or adopt albuminuria as an endpoint in clinical trials (48).

Presently, there is substantial variability in the approach to assessment of albuminuria or proteinuria in the clinical setting. Albumin is the dominant protein in most cases of severe glomerular injury and is the recommended measure for early diabetic nephropathy. Measurement of albuminuria instead of total protein may, however, miss cases of kidney disease associated with multiple myeloma, in which filtered light chains may be the dominant protein. Total protein measurement is unlikely to be standardized, given the diversity of proteins found in the urine. Another question is how to measure and report albuminuria or proteinuria. Twenty-four–hour urine collections are generally considered the gold standard for albumin or protein quantification, but this procedure has important limitations owing to frequent errors in completeness of collection. As a result, many practitioners rely largely on ratios of urinary albumin (or protein) to creatinine on random

urine samples for assessment; when expressed as identical units for both the numerator and denominator (such as mg/dL per mg/dL), the ratio approximates the amount of albumin (or protein) in grams excreted in 24 h. First morning void specimens are preferred, but may not be easily attained in clinical practice (49). Normalization to the urine creatinine concentration is a technique used to attempt to account for the wide range of urinary flow rates across and within individuals but implicitly assumes constant creatinine excretion of approximately 1 gm per day across measurements (43). Currently, there are no reference measurement procedures for urinary albumin and no reference materials for either albumin or creatinine in urine (50). There is an ongoing effort by the NKDEP and IFCC to standardize the measurement and reporting of urinary albumin that promises to clarify these issues in the near future (5, 50).

Post hoc analyses of a subset of participants in the RENAAL (Reduction of Endpoints in Non Insulin Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan) trial compared 24-h urine protein, 24-h urine albumin, and albumin:creatinine ratios for their association with renal function decline (51). The investigators found that the albumin:creatinine ratio was the best measure to predict renal events in patients with type 2 diabetes and nephropathy. Likely reasons for the finding include variability in completeness of 24-h urine collections and the prognostic significance of urinary creatinine excretion itself (52) owing to its association with biologically important variables such as muscle mass and nutritional adequacy. In summary, albuminuria or proteinuria adds importantly to risk stratification of individuals with and at risk for CKD. Albumin:creatinine ratio, preferably in first morning voids, is the preferred test in patients with diabetes mellitus. Protein:creatinine ratio may be preferred in non-diabetic individuals. Twenty-four hour samples are not generally necessary except in select circumstances (e.g., the need for precise determination of albumin or protein excretion rate in longitudinal care of patients with glomerular disease and heavy proteinuria in whom clinical decision-making may be influenced).

Renal Structural and Functional Imaging

Ultrasonography of the kidneys is important in the assessment of patients with established or suspected acute or CKD. Kidney size, echogenicity, cortical thinning, and the presence/absence of hydronephrosis can be readily established with ultrasound. More sophisticated structural imaging by use of MRI may be useful in patients with autosomal dominant polycystic kidney disease to estimate the rate of cyst growth and renal function decline (53). GFR measurement can also be done by using several protocols based on dynamic computed tomography and MRI (54). Such approaches are appealing because they have the unique ability to provide details regarding structure, perfusion, and function simultaneously. In addition, single kidney GFR and split function determinations are possible. A current limitation to CT and MRI GFR measurement is the requirement for iodine- and gadolinium-based contrast agents, respectively. Neither may be acceptable in patients with significant CKD secondary to the risk of contrast nephropathy and nephrogenic systemic fibrosis.

Beyond GFR—Measures of Kidney Injury

Recent attention has focused on the early identification of injury to the kidney that may precede—or even be unaccompanied by—a fall in GFR. Just as a fall in cardiac output does not define myocardial infarction, and hypoalbuminemia and coagulopathy do not solely define liver injury, GFR may not be the appropriate or sole metric for assessment of kidney injury. Reliance on renal functional markers like GFR may limit the ability to initiate strategies that may prevent short-term and long-term functional loss. For this purpose, markers of kidney damage or injury may be most appropriate. Over the last decade, intensive investigative efforts have led to the identification and characterization of several urinary and serum markers that appear to be sensitive and specific for kidney injury. Most notable are N-acetyl-β-(D)-glucosaminidase, neutrophil gelatinase associated lipocalin, kidney injury molecule-1, interleukin-18, and liver-type fatty acid binding protein. Further work is needed to fully determine the utility of these markers, although there is much enthusiasm that they will enhance the understanding of kidney pathophysiology and aid in the development of targeted interventions to ameliorate injury and prevent functional decline. A full discussion of these markers is beyond the scope of this review; however, the reader is referred to excellent recent reviews by Siew et al. (55) and Fassett et al. (56), which detail the current status of these biomarkers in AKI and CKD respectively.

In addition, increased urinary concentrations of filtered low molecular weight proteins, including β_2-microglobulin, α_1-microglobulin, cystatin C, and retinol-binding protein, are reflective of a defect in tubular reabsorptive pathways, which may occur in the setting of acute tubular damage. In general, specificity of these markers for acute injury may be suboptimal because increased urinary concentrations can be seen in several other settings, most notably significant glomerular proteinuria (saturated reabsorptive pathways) and chronic tubulopathies (defective reabsorptive pathways). Table 5 lists several measures of kidney function currently available or in development.

Beyond GFR—Assessing Other Aspects of Kidney Function

Filtration of waste products from the circulation is a life-sustaining function of the kidney, but not the only one. The complications of AKI and CKD are protean and affect numerous organ systems: e.g., anemia, bone disease, metabolic acidosis, dysnatremia, and volume overload. Assessment of the kidney's endocrine function (1-α hydroxylation of 25-hydoxyvitamin D), hematologic function (production of erythropoietin), acid–base regulation (urinary acidification, reabsorption of bicarbonate), control of tonicity (water excretion), and volume regulation (sodium and water excretion) are largely inferred once complications ensue. Furthermore, GFR may not serve as an accurate surrogate marker for some of the complications of kidney disease. Hsu and colleagues (57) assessed the cross-sectional associations between GFR (both measured and estimated) and well-known complications of CKD, including anemia, hyperkalemia, metabolic acidosis, and hyperphosphatemia. They found that none of the measures of GFR—including iothalamate clearance—associated strongly with CKD complications and that the relative strengths of association varied with different outcomes, raising the philosophical question of whether measured GFR is truly the appropriate gold standard. Whether and how to assess the

multidimensional aspects of kidney function in clinical practice remains an unresolved question.

Conclusion

Kidney function is most commonly assessed by estimating GFR by use of serum creatinine. Other endogenous filtration markers have been proposed, including cystatin C and BTP, and may be superior to creatinine for GFR estimation, early detection of AKI, and estimation of prognosis. GFR may be directly measured by use of urinary or plasma clearance of exogenous filtration markers. Direct measurements of GFR are typically reserved for research settings or rare clinical circumstances when endogenous filtration markers may be expected to be unreliable or when precise GFR determination is necessary (e.g., kidney donation from a donor with marginal eGFR). Urinary albumin or protein excretion is a complementary test of kidney function and provides additional independent information on renal and cardiovascular prognosis. Novel biomarkers of kidney injury and function hold the promise of modernizing the diagnostic approach to acute and chronic kidney disease, but additional research is required before they can be introduced into clinical practice.

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Table 1

Classification of chronic kidney disease.[a]

Stage	Description	GFR, mL · min^{-1} · (1.73 m^2)$^{-1}$
I	Kidney damage (defined as structural or functional abnormalities) with GFR ≥90	≥90
II	Kidney damage with mildly decreased GFR	60–89
III	Moderately decreased GFR	30–59
IV	Severely decreased GFR	15–29
V	Kidney failure	<15 (or dialysis)

[a]CKD is defined as either kidney damage or GFR <60 for ≥3 months. Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies.

Table 2

Definition of acute kidney injury: Acute Kidney Injury Network (AKIN) criteria.

Stage	Serum creatinine criteria	Urine output criteria
1	Increase in serum creatinine of ≥0.3 mg/dL (≥26.4 μmol/L) or increase to ≥150%–200% (1.5- to 2-fold) from baseline	<0.5 mL · kg^{-1} · h^{-1} for >6 h
2	Increase in serum creatinine to >200%–300% (>2- to 3- fold) from baseline	<0.5 mL · kg^{-1} · h^{-1} for >12 h
3	Increase in serum creatinine to >300% (>3-fold) from baseline [or serum creatinine of ≥4.0 mg/dL (≥354 μmol/L) with an acute increase of at least 0.5 mg/dL (44 μmol/L)]	<0.3 mL · kg^{-1} · h^{-1} for 24 h or anuria for 12 h

Table 3

Definition of AKI: risk, injury, failure, loss, end-stage renal disease (RIFLE) criteria.

Stage	Serum creatinine criteria	Urine output criteria
Risk	Increase in serum creatinine to ≥150%–200% (1.5- to 2-fold) from baseline or GFR decrease >25%	<0.5 mL · kg^{-1} · h^{-1} for >6 h
Injury	Increase in serum creatinine to ≥200%–300% (2- to 3-fold) from baseline or GFR decrease >50%	<0.5 mL · kg^{-1} · h^{-1} for >12 h
Failure	Increase in serum creatinine to ≥300% (3-fold) from baseline or GFR decrease >75%	<0.3 mL · kg^{-1} · h^{-1} for 24 h or anuria for 12 h
Loss	Persistent AKI = complete loss of renal function >4 weeks	
ESRD	End-stage renal disease	

Table 4

Equations for estimating GFR.[a]

Name	Equation
Adults	
Cockroft–Gault	eCrCl[b] (mL/min) = (140 − age in years) × (weight in kilograms/72 × SCr) × (0.85 if female)
MDRD (4-variable, not IDMS-traceable)	eGFR [mL · min^{-1} · (1.73 m^2)$^{-1}$] · 186 × (SCSr)$^{-1.154}$ × (age in years)$^{-0.203}$ × (0.742 if female) × (1.212 if African American)
MDRD (IDMS-traceable creatinine)	eGFR [mL · min^{-1} · (1.73 m^2)$^{-1}$] = 175 × (Scr)$^{-1.154}$ × (age in years)$^{-0.203}$ × (0.742 if female) × (1.212 if African American)
CKD-EPI (IDMS traceable)	eGFR [mL · min^{-1} · (1.73 m^2)$^{-1}$] = 141 × min (Scr/κ,1)$^{\alpha}$ × max(Scr/κ,1)$^{-1.209}$ × 0.993$^{\text{age}}$ × (1.018 if female) × (1.159 if African American), where κ is 0.7 for females and 0.9 for males, α is −0.329 for females and −0.411 for males, min indicates the minimum of S_{cr}/κ or 1, and max indicates the maximum of S_{cr}/κ or 1]
Children	
Modified Schwartz	eGFR [mL · min^{-1} · (1.73 m^2)$^{-1}$] = (0.413 × height in centimeters)/(Scr)

[a] For all equations listed, serum creatinine (SCr) is in milligrams per deciliter.

[b] eCrCl, estimated Cr clearance; IDMS, isotope dilution mass spectrometry; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration.

Table 5

Markers of renal function.

Marker	Description	Method	Limitations
Endogenous Markers			
Blood urea nitrogen	Nitrogenous end product of protein metabolism Functional marker	Blood sampling	Reabsorbed at variable rates Variable generation rate Levels dependent on renal and nonrenal factors
Creatinine	Byproduct of muscle breakdown Functional marker	Blood sampling Urinary clearance Equation to estimate GFR	Secreted at variable rates Significant variability in interpersonal generation Decreased sensitivity for small decreases in GFR
Cystatin C	Filtered low molecular weight protein Functional marker Decreased proximal tubular reabsorption in AKI	Blood/urine sampling Equation to estimate GFR	Limited availability Requires assay standardization
β_2-Microglobulin	Filtered low molecular weight protein Functional marker Decreased proximal tubular reabsorption in AKI	Blood/urine sampling	Suboptimal specificity as marker of GFR Instability may limit utility of urinary sampling
BTP	Filtered low molecular weight protein Functional marker	Blood sampling Equation to estimate GFR	Limited availability Requires assay standardization
Urinary albumin	Prognostic marker of kidney disease	Urine sampling	May be increased in nondisease states
N-acetyl-β-(D)-glucosaminidase	Increased urinary excretion in AKI	Urine sampling	Suboptimal specificity for AKI in some clinical settings
Kidney injury molecule-1	Upregulated in AKI Potential marker of CKD progression	Urine sampling	Still under investigation to assess diagnostic thresholds, sensitivity/specificity, implications for clinical care
Neutrophil gelatinase associated lipocalin	Upregulated in AKI Potential marker of CKD progression	Urine/blood sampling	Still under investigation to assess diagnostic thresholds, sensitivity/specificity, implications for clinical care
Interleukin-18	Upregulated in AKI	Urine sampling	Still under investigation to assess diagnostic thresholds, sensitivity/specificity, implications for clinical care
Liver-type fatty acid binding protein	Increased translocation to tubular lumen in AKI marker of CKD progression	Urine sampling	Still under investigation to assess diagnostic thresholds, sensitivity/specificity, implications for clinical care
Exogenous			
Inulin	Inert polysachharide Gold standard for GFR measurement	Urinary clearance	Difficult to perform Expensive Limited supply
Iohexol	Radiographic contrast agent	Plasma clearance	Requires HPLC assay Contraindicated in those with iodine allergy
Iothalamate	Radiographic contrast agent Radionuclide	Plasma clearance	Nonradioactive assay requires HPLC Contraindicated in those with iodine allergy

Marker	Description	Method	Limitations
			Radiolabeled iothalamate requires facilities for storage/ disposal of radioactive materials
^{99m}Tc-DTPA	Radiopharmaceutical agent	Plasma clearance	Not available in US Requires facilities for storage / disposal of radioactive materials
^{51}Cr-EDTA	Radiopharmaceutical agent	Plasma clearance	Requires facilities for storage/ disposal of radioactive materials
Other			
Iodinated contrast material	Functional imaging	Computed tomography	Radiation exposure Risk for contrast-related nephrotoxicity Gadolinium exposure in magnetic resonance–based studies
Gadolinium contrast material	Functional imaging	Magnetic resonance	Risk of nephrogenic systemic fibrosis in those with advanced CKD or AKI
Carbostyril124–DTPA-Eu	Fluorescence-based marker	Optical monitoring	Requires clinical validation
FITC-sinistrin	Fluorescence-based marker	Transcutaneous optical monitoring	Requires clinical validation
FITC-inulin + Texas Red dextran	Fluorescence-based markers	Optical ratiometric analysis	Requires clinical validation