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Measured GFR as a Confirmatory Test for Estimated GFR

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ABSTRACT

Clinical assessment of kidney function is central to the practice of medicine. GFR is widely accepted as the best index of kidney function in health and disease, and accurate values are required for optimal decision making. Estimated GFR based on serum creatinine is now widely reported by clinical laboratories, and in most circumstances, estimated GFR is sufficient for clinical decision making. GFR estimates may be inaccurate in the non–steady state and in people in whom non-GFR determinants differ greatly from those in whom the estimating equation was developed. If GFR estimates are likely inaccurate or if decisions based on inaccurate estimates may have adverse consequences, a measured GFR is an important confirmatory test. Endogenous creatinine clearance is the most common method used to measure GFR in clinical practice but may be difficult to obtain or fraught with error. We review methods for GFR measurement using urinary and plasma clearance of exogenous filtration markers and focus on urinary clearance of iothalamate and plasma clearance of iohexol compared with inulin clearance. We suggest plasma clearance of nonradioactive markers be more widely implemented in clinical settings. Further research is necessary on the impact of the use of measured GFR as a confirmatory test.

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Clinical assessment of kidney function is central to the practice of medicine. GFR is widely accepted as the best index of kidney function in health and disease, and accurate values are needed for optimal decision making in many clinical settings. Estimated GFR (eGFR) based on serum creatinine is now widely reported by clinical laboratories and is available in most clinical encounters as a "first line" test of kidney function.[1] In other fields of medicine, first line tests are followed by more accurate confirmatory tests when needed. Measured GFR (mGFR) using urinary or plasma clearance of exogenous filtration markers is considered the gold standard for evaluation of kidney function but is not routinely available because of the complexity of measurement protocols. Instead clinicians usually rely on endogenous creatinine clearance. However, timed urine collections are difficult to obtain and fraught with error. We suggest that despite the complexity, GFR should be more often measured as a confirmatory test in clinical practice. In this review, we will describe indications for measured GFR and describe its interpretation, including the techniques and strengths and limitations of various protocols. We focus our discussion on urinary clearance of inulin as the gold standard method and two alternative protocols: urinary clearance of iothalamate, the method most commonly used in the past two decades in the United States and in the development of recent GFR estimating equations, and plasma clearance of iohexol, which may be more readily implemented in most clinical settings.

The level of GFR is only one parameter by which kidney disease is evaluated. Clinical decisions are also based on the cause of kidney disease, presence or absence of complications, risk factors for rapid progression and comorbid conditions, and the presence of albuminuria. Nevertheless, the level of GFR and its magnitude of change over time are vital to the detection of kidney disease, understanding its severity and for making decisions about diagnosis, prognosis, and treatment (Table 1).

GFR is most commonly estimated from serum creatinine using the Modification of Diet in Renal Disease (MDRD) Study equation.[1,2] In most stable outpatients without serious comorbid conditions, the MDRD Study equation provides GFR estimates that are sufficiently accurate for clinical decision making. However, large differences between mGFR and eGFR can be observed in other populations and clinical settings.[3] New equations based on creatinine, as well as novel filtration markers, such as cystatin C, will likely improve the accuracy in some populations, but the likelihood of error will remain.[4,5] Recognition of the strengths and limitations of any estimating equation, and the clinical settings when GFR estimates are likely to be inaccurate, will enable identification of

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Table 1. Clinical conditions where assessment of GFR is important

Clinical Decisions	Current Level of GFR	Change in Level of GFR
Diagnosis	Detection of CKD	Detection of AKI
	Evaluation for kidney donation	Detection of CKD progression
Prognosis	Risk of CKD complications	Risk for kidney failure
	Risk for CVD	
	Risk for mortality	
Treatment	Dose and monitoring for medications cleared by the kidney	Treatment of AKI
	Determine safety of diagnostic tests or procedures	Monitoring drug toxicity
	Referral to nephrologists	
	Referral for kidney transplantation	
	Placement of dialysis access	

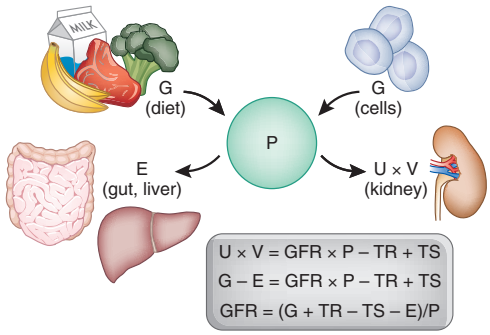

Figure 1. Determinants of the serum level of endogenous filtration markers. The plasma level (P) of an endogenous filtration marker is determined by its generation (G) from cells and diet, extrarenal elimination (E) by gut and liver, and urinary excretion (UV) by the kidney. Urinary excretion is the sum of filtered load (GFR × P), tubular secretion (TS), and reabsorption (TR). In the steady state, urinary excretion equals generation and extrarenal elimination. By substitution and rearrangement, GFR can be expressed as the ratio of the non-GFR determinants (G, TS, TR, and E) to the plasma level.

those patients in whom a measured GFR should be considered.

NON-GFR DETERMINANTS OF SERUM LEVELS OF ENDOGENOUS FILTRATION MARKERS

Generation, renal excretion (filtration, secretion, and reabsorption), and extrarenal elimination determine serum levels of endogenous filtration markers (Figure 1). Estimating equations use easily measured clinical variables as surrogates for these unmeasured physiologic processes and provide more accurate estimates than the serum level alone.[6] However, by design, equations capture only the average relationship of the surrogates to some of these physiologic processes, leading to error in some individuals.

Creatinine-based estimating equations include age, gender, race, or weight as surrogates for differences in creatinine generation from muscle mass (Table 2).[2,7] People who are at the extremes of muscle mass and diet, who are malnourished or have a reduction in muscle mass from illness or amputation, who are of different races or ethnicities than included in studies used for development of the equations, or who have changes in the non-GFR determinants over time are most likely to have large differences between mGFR and eGFR.[6,8–10]

One of the challenges with the introduction of a novel filtration marker into clinical practice is that the non-GFR determinants may not be well understood, potentially limiting their interpretation in clinical practice. For example, it is now well recognized that there are many factors associated with the serum level of cystatin C other than GFR, but the mechanisms for these associations are not well understood.[11]

NON–STEADY STATE

Serum levels of endogenous filtration markers, and eGFR derived from these markers, are expected to be an accurate index of mGFR only in the steady state. Figure 2 shows the hypothetical change in levels of a filtration marker and estimated GFR based on that marker after an acute change in GFR.[12] In the non–steady state, the rate and direction of change in the level of the filtration marker and in eGFR reflect the magnitude and direction of the change in GFR but do not accurately reflect the level of GFR. As shown in Figure 2, after a fall in GFR, the decline in eGFR is less than the decline in GFR, and eGFR thus exceeds GFR. Conversely, after a rise in GFR, the rise in eGFR is less than the rise in GFR, and eGFR is thus less than GFR. As the serum level approaches the new steady state, eGFR approaches GFR, and the level of the filtration marker varies inversely with GFR. The rate of rise in the marker reflects not only the severity of the reduction in GFR but also the non-GFR determinants.

CLINICAL SCENARIOS WHEN ACCURATE ASSESSMENTS MAY BE NECESSARY

In most circumstances, eGFR is sufficient for clinical decision making (Table 1). However, for patients in whom GFR estimates based on serum creatinine are likely to be inaccurate or in clinical circumstances in which decisions based on inaccurate estimates may have adverse consequences, mGFR may be helpful. Below, we describe clinical situations in general medicine and nephrology where measurement of GFR should be considered (Table 3).

Chronic Illness

All creatinine-based equations provide inaccurate estimates when used in people with abnormal levels of muscle mass. This is most relevant in chronically ill or hospitalized patients with reduced muscle mass. In these settings, eGFR is systematically higher than mGFR, and reliance on eGFR could lead to medical errors in this high-risk population, in particular, toxicity from excess medication doses and inappropriate use of imaging tests, as described below.

Drug Dose Adjustment

The kidneys excrete many drugs, and some medicinals have a narrow therapeutic window. eGFR is sufficient for adjustment of many medications, but mGFR should be considered before initiation of prolonged and potentially toxic therapy, such as cancer chemotherapy. Possibly, toxicities of some therapeutic agents could be reduced, and therapeutic efficacy improved, if more accurate GFR values were used to determine dose. This requires further study.

Imaging Tests

Contrast agents containing iodine and gadolinium have heightened toxicity at low GFR, requiring individual decision making regarding risks and benefits of imaging tests. Current recommendations are to avoid exposure to gadolinium and to consider preventive measures before iodine exposure in patients with reduced GFR. mGFR might allow improved decision making in patients in whom GFR estimates are unreliable.

Monitoring Impact or Toxicity of Treatments

Nephrotoxicity is a major concern in the use of drugs. However, drugs may also affect non-GFR determinants of serum creatinine by decreasing generation or inhibiting tubular secretion or extrarenal elimination. In addition, drugs may affect overall health status, leading to changes in creatinine generation from diet or muscle mass. In these circumstances, measured GFR is necessary to distinguish drug effects on serum creatinine caused by GFR *versus* non-GFR determinants.

Table 2. Non-GFR determinants of creatinine

Factor	Effect on Serum Creatinine Independent of GFR		Accounted for in GFR Estimating Equations
	Direction	Mechanism	
Age	Decrease	Generation	Yes
Female gender	Decrease	Generation	Yes
Race		Generation	
African American	Increase		Yes
Hispanics	Decrease		No
Asian	Increase/Decrease		Yes
Body habitus		Generation	
Muscular	Increase		No
Amputation	Decrease		No
Obesity	No change		No
Chronic illness		Generation	
Malnutrition, inflammation, deconditioning	Decrease		No
Neuromuscular diseases	Decrease		No
Liver disease	Decrease		No
HIV	Decrease?		No
Diet		Generation	
Vegetarian diet	Decrease		No
Ingestion of cooked meat	Increase		No
Medications			
Cimetidine	Increase	Tubular secretion	No
Trimethroprim	Increase	Tubular secretion	No
Antibiotics	Increase	Extrarenal elimination	No

Interpretation of Symptoms of Kidney Failure

Timing of access placement, preemptive transplantation, and initiation of dialysis are generally determined based on an eGFR and patient symptoms. However, symptoms of uremia are nonspecific. In patients with discrepancy between severity of reduction in eGFR and symptoms, it may be helpful to measure GFR.

Monitoring Kidney Transplant Recipients

Interpretation of changes in eGFR after kidney transplantation can be challenging. Rejection and nephrotoxicity are constant threats that require early detection and treatment. At the same time, there are multiple factors that affect non-GFR determinants of serum creatinine, such as liberalization of diet, use of trimethoprim, and muscle wasting effects of corticosteroids. mGFR may be necessary in complex cases in which it is suspected that both GFR and GFR determinants of serum creatinine are changing.

Kidney Donation

The MDRD Study equation systematically underestimates mGFR at higher levels.[13] Improved equations are likely to diminish the average underestimation, but errors will not be eliminated entirely. If the eGFR is low in an otherwise healthy potential kidney donor, mGFR should be considered.

INTERPRETATION

Normal values for mGFR in whites are ~130 ml/min per 1.73 m^2 for young men and 120 ml/min per 1.73 m^2 for young women.[14,15] Normal values show considerable variation among individuals, with measured values typically adjusted for body size. Day to day variability in mGFR is affected by protein intake, exercise, and diurnal variation.

The gold standard for the measurement of GFR is urinary clearance of an ideal filtration marker, defined as a substance that is freely filtered at the glomer-

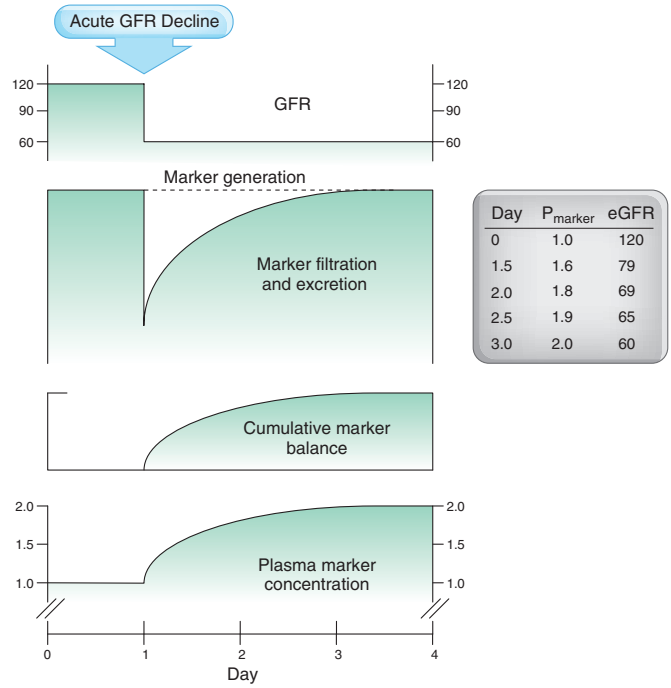

Figure 2. Effect of an acute GFR decline on generation, filtration, excretion, balance, and serum level of endogenous filtration markers. After an acute GFR decline, generation of the marker is unchanged, but filtration and excretion are reduced, resulting in retention of the marker (a rising positive balance) and a rising plasma level (non–steady state). During this time, eGFR is lower than GFR. Although GFR remains reduced, the rise in plasma level leads to an increase in filtered load (the product of GFR times the plasma level) until filtration equals generation. At that time, cumulative balance and the plasma level plateau at a new steady state. In the new steady state, eGFR approximates mGFR. GFR is expressed in units of milliliter per minute per 1.73 m^2. Tubular secretion and reabsorption and extrarenal elimination are assumed to be zero. Modified and reproduced with permission from Kassirer JP, *N Engl J Med* 285: 385–389, 1971.

Table 3. Indications for measured GFR

Extremes of age and body size
Severe malnutrition or obesity
Disease of skeletal muscle
Paraplegia or quadriplegia
Evaluation for kidney donation
Vegetarian diet
Before administration of prolonged courses of toxic medications

ulus, neither reabsorbed, secreted, synthesized, or metabolized by the tubules, and does not alter the function of the kidney. Inulin, a 5200-D, inert, uncharged polymer of fructose, is the only known ideal filtration marker. The classic clearance method of Homer Smith includes fasting conditions in the morning, a continuous intravenous infusion, multiple clearance periods requiring repetitive blood and urine collections over 3 h, oral water loading to stimulate diuresis, bladder catheterization to assure complete urine collection, and careful timing of blood sampling at the midpoint of the urine collection.[14] However, inulin is difficult to handle, and the procedures are invasive. Because of these disadvantages, we use alterative clearance methods and filtration markers. Table 4 summarizes the strengths and limitations of the gold standard method, as well as other the clearance methods and markers.

All other filtration markers deviate from ideal behavior, and clearance measurements are difficult to perform; thus, values for mGFR usually contain an element of error, which differentiates it from true physiologic GFR. Bias generally reflects systematic differences in renal handling, extrarenal metabolism, or assay of the filtration marker. This bias is assessed experimentally by comparison to an ideal filtration marker relevant for assessing level of GFR in ranges important for clinical decision making. Imprecision generally reflects random error in performance of the clearance procedure or assay of the filtration marker. Measurements performed under standard conditions will minimize biologic variation and will reduce the likelihood of random errors. Precision is assessed by repeated measurement over a short time. Imprecision in mGFR is relevant for assessment of change in GFR over time. In an individual patient, bias and imprecision both affect the measured level and must be considered in the interpretation of mGFR. To evaluate the extent of the available literature and to provide data for this discussion, we performed a systemic review of all studies that compared simultaneous measurements of iohexol, iothalamate, and inulin or repeated measurements of these markers using the same protocol (Table 5).[16–43] The gray shaded boxes in Table 5 show the studies that report repeated measurements using the same protocol. Other markers and their comparison to inulin are also discussed below.

CLEARANCE METHODS

Urinary Clearance

Urinary clearance is the most direct method for measurement of GFR. Clearance is computed as the urine concentration of the exogenous or endogenous filtration marker, multiplied by the volume of the timed urine sample, and divided by the average plasma concentration during the same time period.

Measurement of the clearance of an endogenous filtration marker, such as creatinine, is performed in virtually every clinical center. A long urinary collection period—6 to 24 h—is used to avoid the requirement for water loading, and in the steady state, a single blood sample obtained either at the beginning or end of the collection period may be assumed to represent the average serum concentration during the urine collection. Timed collections are subject to errors caused by inaccurate record of time and

Table 4. Strengths and limitations of GFR measurement methods and markers

Approach	Strengths	Limitations
Methods		
Urinary clearance		
Bladder catheter and continuous intravenous infusion of marker	Gold standard method	Invasive
Spontaneous bladder emptying	Patient comfort	Possibility of incomplete bladder emptying
	Less invasive	Low flow rates in people with low levels of GFR
Bolus administration of marker	Shorter duration	Rapidly declining plasma levels at high levels of GFR
		Longer equilibration time in extracellular volume expansion
24-h urinary collection	Can be performed at home	Cumbersome
		Prone to error
Plasma clearance	No urine collection needed	Overestimation of GFR in extracellular volume expansion
	Potential for increased precision	Inaccurate values with one-sample technique, particularly at lower GFR levels
		Longer duration of plasma sampling required for low GFR
Nuclear imaging	No urine collection or repeated blood samples needed	Less accurate
	Relatively short duration	
Markers		
Inulin	Gold standard	Expensive
	No side effects	Difficult to dissolve and maintain into solution
		Short supply
Creatinine	Endogenous marker, no need for administration	Secretion which can vary among and within individuals
	Assay available in all clinical laboratories	
Iothalamate	Inexpensive	Probable tubular secretion
	Long half-life	Requirement for storage, administration, and disposal of radioactive substances when ^{125}I used as tracer
		Use of non-radioactive iothalamate requires expensive assay
		Cannot be used in patients with allergies to iodine
Iohexol	Not radioactive	Possible tubular reabsorption or protein binding
	Inexpensive	Use of low doses requires expensive assay
	Sensitive assay allows for low dose	Cannot be used in patients with allergies to iodine
		Nephrotoxicity and risk for allergic reactions at high doses
EDTA	Widely available in Europe	Probable tubular reabsorption
		Requirement for storage, administration, and disposal of radioactive substances when ^{51}Cr is used as tracer
DTPA	Widely available in the United States	Requirement for storage, administration, and disposal of radioactive substances when ^{99m}Tc used as tracer
	New sensitive and easy to use assay for gadolinium	Requires standardization for ^{99m}Tc
		Dissociation and protein binding of ^{99m}Tc
		Concern for NSF when gadolinium is used as the tracer

Table 5. Summary of comparison studies of GFR measured using inulin, iothalamate, and ioexhol

Marker			IOHEXOL			IOTHALAMATE							INULIN
Administration			BIV	BIV	BIV	BIV	BIV	CSC	CSC	CIV	CIV	BSC	CIV
Clearance method			Plasma (1)	Plasma (2)	Urinary	Plasma	Urinary	Plasma	Urinary	Plasma	Urinary	Urinary	Urinary
Marker	Admin	Clear											
INULIN	CIV	Urinary	4 (22–41)[16–19]	1 (41)[16]	1 (30)[17]						7 (15–84)[20–26]	5 (22–100)[26–30]	2 (12–40)[31,32]
IOTHALAMATE	BSC	Urinary										1 (957)[33]	
	CIV	Urinary								1 (212)[34]			
	CIV	Plasma											
	CSC	Urinary	2 (41–52)[35,36]					1 (50)[37]	1 (17)[37]				
	CSC	Plasma						1 (17)[37]					
	BIV	Urinary				1 (19)[38]							
	BIV	Plasma											
IOHEXOL	BIV	Urinary	1 (30)[17]										
	BIV	Plasma (2)	4 (36–87)[16,39–41]										
	BIV	Plasma (1)	3 (24–41)[39,42,43]										

Numbers in each cell indicate the number of studies, with the range of patients included in these studies indicated in parentheses. Plasma (1) indicates plasma clearance calculated using a single compartment model; Plasma (2) indicates plasma clearance calculated using a two compartment model. B, bolus; C, continuous; IV, intravenous; SC, subcutaneous.

complete urine collection. Indeed, in the MDRD Study, measured creatinine clearance was not more accurate than eGFR using the MDRD Study equation.[33] Averaging over repeated measurements may minimize the impact of error but adds to patient burden. One of the limitations of cystatin C is that it is catabolized and reabsorbed by the tubules.[44,45] As such, its urinary clearance cannot be measured.

For an exogenous filtration marker, multiple (2 to 4) 20- to 30-min urine collections are obtained after administration of the marker, clearance is computed for each urine collection period, and the results are averaged.[46] Advantages include a relatively short duration of time, and comparison of the individual periods allows for an assessment of quality of test results. The marker is administered by intravenous bolus or bolus subcutaneous injection. Subcutaneous injection allows for a slower release of the marker into the circulation and more constant plasma levels.[26,27,33]

In patients with high GFR, the marker is rapidly excreted. Administration of water before and during the protocol is necessary to stimulate urine flow to allow completion of urine collections while the marker concentration remains above the detection limit of the assay. Spontaneous voiding is used almost exclusively, which limits its use in populations with impaired urinary incontinence or retention, such as the elderly or children with urinary tract abnormalities and which increases risk for error caused by incomplete urine collections.

The classic study by Davies and Shock[31] reported an SD of the range of 4.9 to 9 ml/min per 1.73 m^2 in normal individuals (mean GFR, ~90 ml/min per 1.73 m^2) for urinary clearance of inulin measured twice over 2 d. Another study of urinary clearance of inulin reported a coefficient of variation of 11.3%.[32] In the MDRD Study, the median coefficient of variation for repeated measurement of urinary clearance of iothalamate using bolus subcutaneous injection was 6.3% over 3 mo, whereas it was 18.7% in another study where iothalamate was administered using continuous subcutaneous infusion.[33,37]

Plasma Clearance

There is increasing interest in measuring plasma clearance to avoid inconvenience and errors from timed urine collections, and this methodology is of increasing importance given the aging population. In principle, plasma clearance should be unbiased and more precise compared with urinary clearance except for markers that undergo extrarenal elimination. GFR is calculated from plasma clearance after a bolus intravenous injection of an exogenous filtration marker, with clearance computed from the amount of the marker administered divided by the area under the curve of plasma concentration over time. The decline in serum levels is secondary to the immediate disappearance of the marker from the plasma into its volume of distribution (fast component) and to renal excretion (slow component). This is best estimated using a two-compartment model that requires blood sampling early (usually two to three time points until 60 min) and late (one to three time points from 120 min forward).

The major disadvantage of plasma clearance is the length of time (~5 h) needed to determine the disappearance curve, with an even longer time needed in people with very low GFR (8 to 10 h).[16] Shorter time periods may lead to overestimation of GFR throughout the GFR range.[47] Second, it may be difficult to obtain repeated blood samples in people with poor vascular access. To minimize the need for repeated blood samples, an equation has been developed to approximate the fast component, allowing the decline to be estimated using only late samples.[40,48] Third, a large volume of distribution, such as edematous conditions,

prolongs the initial component, leading to an overestimation of GFR.[38]

Studies comparing urinary and plasma clearance of either iothalamate or iohexol show high agreement, although some studies showed that plasma clearance slightly overestimates urinary clearance at lower levels of GFR (Table 5).[17,34] In studies of repeated measurements of plasma clearance of iothalamate or iohexol, the coefficient of variation ranged from 5.6 to 11.5%,[37,39,42,43] similar to the variation observed with urinary clearance reported above. More studies are necessary to determine the precision of these methods.

External Counting and Imaging

GFR can also by measured by counting of a radioactive exogenous filtration marker over the kidneys and bladder. This technique can be combined with renal imaging, usually using ^{99m}Tc-DTPA, and is useful for determination of split kidney function.[49,50] Several studies indicate poor correlation of ^{99m}Tc-DTPA dynamic renal imaging with simultaneous urinary or plasma clearance, reflecting both bias and imprecision and lesser accuracy than eGFR.[51–53] Currently, magnetic resonance imaging is being investigated for measurement of GFR. Many protocols are in use that will need consolidation before introduction into clinical practice.[54,55]

EXOGENOUS FILTRATION MARKERS

Iothalamate

Iothalmate is commonly administered as a radioactive iodine label for ease of assay after small doses but can also be administered in its nonradioactive form and measured using HPLC without impact on its filtration properties. In the radioactive form, it is most commonly administered using bolus subcutaneous injection. ^{125}I-Iothalamate has been widely adopted for measurement of GFR. To block thyroidal uptake, cold iodine is administered at the time of ^{125}I-iothalmate administration, thus precluding its use in people with known allergies to iodine, such as shellfish or iodinated contrast media. Most[20,21,26,27,29,30] but not all[22–25] studies comparing urinary clearance of iothalamate to inulin showed a small positive bias, probably because of tubular secretion of iothalamate (Table 5).

Iohexol

Concern about radiation led to the use of the nonradioactive radiographic contrast agent iohexol.[40] Iohexol is administered most often using bolus intravenous injection for plasma clearance but could be used for urinary clearance as well. Other advantages include low expense, wide availability, stability in biologic fluids, and rare adverse reactions when given as a small dose (5 ml of 300 mg/ml iodine) when assayed with a sensitive HPLC assay.[17,43,56,57] Major limitations are the complexity and expense of the HPLC assay. Iohexol can also be assayed using x-ray fluorescence but is less sensitive than HPLC, necessitating administration of significantly larger doses of iohexol (10 to 90 ml of 300 mg/ml iodine).[16,17,35] Four small studies have compared plasma clearance of iohexol to urinary clearance of inulin (Table 5). Two of the studies showed a small underestimate of inulin clearance, suggesting tubular reabsorption or protein binding.[16–19] Two studies compared plasma clearance of iohexol using a one-compartment model with blood sampling to 240 min to urinary clearance of iothalamate. Both studies suggested a high correlation between the two methods (90 to 95%).[35,36]

Other Filtration Markers

The ^{51}Cr-EDTA marker is not commercially available in the United States, but there is an extensive European experience.[48,58–60] The urinary clearance of ^{51}Cr-EDTA consistently underestimates inulin clearance by 5 to 15% in most, although not all, studies, suggesting tubular reabsorption.[48]

Diethethylenetriaminopenta-acetic acid (DTPA), an analog of EDTA, usually labeled with ^{99m}Tc, is available in the United States. Advantages include a short half-life (6 h) that minimizes radiation exposure, high counting efficiency of ^{99m}Tc, and common used in most nuclear medicine departments.[49,61] DTPA is thought to be freely filtered at the glomerulus, with minimal tubular reabsorption, but may undergo extrarenal elimination. Its major limitation is the potential for dissociation of ^{99m}Tc from DTPA and binding to plasma proteins, leading to underestimation in GFR. The extent of dissociation is not predictable, leading to imprecision and bias. In addition, chelating kits and technetium generators are not standardized in the United States, making comparisons of mGFR among different institutions difficult.

The magnetic resonance imaging contrast agents, gadolinium-DTPA or gadolinium-DOTA, have recently been discussed as novel exogenous filtration markers because, in part, of the wide availability of these agents and their low rate of allergic reactions.[62,63] In addition, a highly sensitive, novel, immunoassay technique is easily performed in most clinical laboratories and needs very low doses (1/40th of dose used for contrast).[64] The recent attention to systemic nephrogenic fibrosis diminishes enthusiasm for this agent in people with lower levels of GFR, but because of the very low dose needed, this reaction is highly unlikely.[65]

CLINICAL RECOMMENDATIONS

There are a variety of differences among markers and clearance methods for GFR measurement compared with the classic method of inulin clearance. However, the bias seems relatively small, and imprecision can be reduced by adherence to standardized protocols, providing accuracy substantially greater than eGFR. Based on the advantages and disadvantages described above, we suggest that plasma clearance of nonradioactive exogenous markers is the most simple to implement by clinical laboratories not already performing GFR measurements.

CONCLUSIONS

GFR estimation is essential to the assessment of kidney disease. GFR estimating

equations provide more accurate estimates from serum markers than serum markers alone and can be used in most clinical encounters, but have serious limitations in some clinical circumstances. mGFR is a reasonable confirmatory test to enhance clinical decision making in these circumstances. Protocols for GFR measurement have been widely tested and are accurate and safe. We suggest that GFR measurement should be more widely used in clinical practice. Nephrologists, in collaboration with clinical laboratories or nuclear medicine departments, should provide leadership in the implementation of GFR measurement protocols in their local institutions. Further research is necessary to assess the impact of mGFR as a confirmatory test in routine clinical practice.

DISCLOSURES

None.

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