

Clinical Decision Making in a Patient with Stage 5 CKD—Is eGFR Good Enough?

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Abstract

The development and widespread use of serum creatinine concentration–based prediction equations to calculate eGFR have been major advances for detection of patients with CKD and the epidemiologic study of CKD and its outcomes. However, these equations as well as those that also incorporate serum cystatin C concentration provide GFR estimates that, although reasonably precise on average, can differ markedly and in clinically important ways from actual GFR. Thus, it is important that clinicians who use these equations for clinical decision-making be familiar with their strengths and weaknesses and have an appreciation of their potential for error. More precise knowledge of actual GFR is important in certain clinical circumstances, including, as presented in this Attending Rounds, patients with stage 5 CKD, in whom decisions regarding dialysis initiation are necessary. Nephrologists should have the ability to accurately determine GFR when needed if clinical circumstances suggest inaccuracy of the calculated eGFR reported by the clinical laboratory.

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Introduction

Mrs. J. J. is a 63-year-old woman with hypertension, obesity, proteinuria, and CKD. A kidney biopsy in the past revealed diffuse global glomerulosclerosis and hypertensive arteriolosclerosis with moderate to severe tubular atrophy and interstitial fibrosis. Her serum creatinine had been stable for several years in the range of 2.42–3.41 mg/dl, with spot urine protein/creatinine ratio of 1.0–1.4. She missed several office appointments; then, she returned for follow-up reporting mild fatigue and slightly diminished appetite but was asymptomatic otherwise. Medications included amlodipine, furosemide, losartan, spironolactone, and ergocalciferol.

Her weight had declined about 2 kg to 79 kg (body mass index [BMI]=31.8). BP was 134/70 mmHg. Physical examination was normal, with no edema or asterixis. Serum creatinine was 4.96 mg/dl, BUN was 37 mg/dl, potassium was 3.7 mmol/L, bicarbonate was 21 mmol/L, calcium was 8.7 mg/dl, phosphorous was 3.7 mg/dl, albumin was 3.7 g/dl, hemoglobin was 10.3 g/dl, urine protein/creatinine ratio was 1.8, and immunoreactive parathyroid hormone was 26.4 pmol/L. Laboratory-reported eGFR was 11 ml/min per 1.73 m².

Discussion

Some measured or calculated assessment of GFR is our standard determination of kidney function for purposes of assessing and categorizing both AKI and CKD. Whole-kidney GFR represents the summation of the single-nephron GFR of all functioning glomeruli. Single-nephron GFR is a function of the balance of transcapillary hydrostatic and oncotic pressures, an ultrafiltration coefficient reflecting the product of glomerular capillary surface area and hydraulic permeability, and renal

plasma flow (1). Despite the well known limitations of creatinine-based assessments of GFR, which date back to the 1920s, their use persists in the absence of a generally acceptable alternative. Contemporary clinical practice guidelines use serum creatinine–based formulas, discussed below, to define eGFR \geq 90 ml/min per 1.73 m² as normal and eGFR $<$ 60 ml/min per 1.73 m² when confirmed with at least two determinations over $>$ 3 months as CKD (2).

On the basis of her serum creatinine, age, and race, this patient has stage 5 CKD or, more precisely, stage G5A3 CKD (2) accounting for both eGFR and albuminuria. In this Attending Rounds, I will address eGFR-based clinical decision-making in adults with advanced (stage 5) CKD. GFR determination in children and adolescents is reviewed elsewhere (3).

Measured GFR—Inulin and Other Exogenous Markers

Inulin is a 5200-D fructose polymer derived originally from roots of the *Inula helenium* plant and more recently, the Jerusalem artichoke (oddly named, because it is a sunflower and is native to certain parts of the United States and Canada but not Jerusalem), chicory, and other plants. It is not protein bound. It is freely filtered at the glomerulus. It is not metabolized, synthesized, secreted, or reabsorbed in the kidneys, and aside from a trivial degree of biliary excretion, it is entirely excreted in the urine (4). The renal or urinary clearance of exogenously administered inulin has been the gold standard for measurement of whole-kidney GFR since its first description by Smith and colleagues (5,6) in 1938.

When asked to define clearance, many physicians will be able to recite the formula for calculating clearance

(“It’s UV/P”) but will not be able to precisely describe what it is. Renal clearance is a concept derived from mass balance principles. For substances that are not synthesized or metabolized by the kidneys, the rate at which a filtered substance is excreted in the urine equals its plasma removal rate. Thus, renal clearance of a substance is conceptualized as the theoretical or virtual volume of plasma from which the substance would need to be completely removed so as to appear in the urine during a defined time period, typically expressed in milliliters per minute. It is calculated as $C_x = U_x V / P_x$, where C_x is renal clearance of substance x , U_x is its urinary concentration, P_x is its plasma concentration, and V is the timed urinary flow rate. For a substance, such as inulin, with the characteristics noted above, it can be shown that its clearance equals GFR, because its filtered load, $(\text{GFR})P_{\text{inulin}}$, equals its urinary excretion over time ($U_{\text{inulin}}V$); hence, $\text{GFR} = U_{\text{inulin}}V / P_{\text{inulin}}$ (1,4). Normal levels of GFR on the basis of inulin clearance studies have been reported to be approximately 130 and 120 ml/min per 1.73 m² in young healthy men and women, respectively. Although the ideal measure of GFR in my patient might be urinary inulin clearance, such studies are cumbersome, they require intravenous infusion of inulin, inulin is not widely available and is expensive, and inulin assays are not standardized.

Other noncreatinine exogenous markers have also been studied to measure GFR on the basis of either renal (urinary) or plasma clearance. The former requires measurement of the substance in both urine and plasma, ideally while at steady-state plasma concentration, whereas the latter measures the disappearance of a substance from plasma over time, typically after a bolus intravenous infusion, without the need for timed urine collections. A recent systematic review analyzed the accuracy of common alternative approaches to measuring GFR using the radioisotopes EDTA (⁵¹Cr-EDTA) and diethylenetriaminepenta-acetic acid (⁹⁹Tc-DTPA) and the iodinated contrast agents iohexol and iothalamate (measured by chemical assay or as the isotope ¹²⁵I-iothalamate) with inulin clearance as the reference test. Using criteria of median bias (systematic difference between measured GFR and eGFR) $\leq 5\%$, mean bias $\leq 10\%$, at least 80% of measurements within $\pm 30\%$ of reference measurements (P_{30}), and at least 50% of measurements within $\pm 10\%$ of reference measurements, renal clearance of iothalamate, renal and plasma clearance of ⁵¹Cr-EDTA, plasma clearance of iohexol, and renal clearance of DTPA and iohexol were determined to be of sufficient accuracy (7). Endogenous creatinine clearance, discussed next, and plasma DTPA clearance, were not. Test performance in patients with very low GFR, such as the patient discussed here, was not evaluated.

One recent systematic review stated that, “In usual practice, an eGFR equation is defined as having sufficient accuracy when at least 75% of the estimates fall within $\pm 30\%$ of the measured GFR” (8). However, when important clinical decisions require knowledge of a patient’s GFR, knowing the actual (measured) GFR as accurately as possible seems preferable to having a ballpark estimate. Unfortunately, if one were to insist on a higher degree of accuracy from these inulin “wannabes”, such as having 90% or more determinations being within 10% of inulin clearance, none would be satisfactory.

Creatinine-Based GFR Measurement

Creatinine is a metabolic product of creatine and phosphocreatine, both of which are found primarily in muscle (9). Despite the historical tenacity of its use, it is now well known that endogenous urinary creatinine clearance does not have acceptable precision for most purposes in clinical practice. Although creatinine shares most of the features that makes inulin an ideal marker of GFR, it fails in one critically important aspect, in that a significant fraction of its urinary excretion results from secretion in the proximal tubule. In normal individuals, creatinine clearance thus exceeds inulin clearance by 10%–20% and in patients with advanced kidney disease, >50%–60% of urinary creatinine may be caused by tubular secretion. Creatinine reabsorption may also occur at very low urine flow rates (9). One interesting recent report actually indicated that fractional excretion of creatinine (using inulin-measured GFR) varied from 0.7 (indicating substantial net creatinine reabsorption) to 1.4 (indicating net secretion) in a kidney transplant cohort (10). Creatinine is also subject to variable elimination through the gastrointestinal tract in individuals with advanced kidney disease. Cimetidine, an H₂-receptor antagonist that inhibits tubular secretion of creatinine, was used in the past to accurately assess GFR using creatinine clearance with reasonable success (11–13). This has fallen out of favor, however, because of, in part, side effects associated with the high doses of cimetidine that were used.

Creatinine use as a GFR marker is further complicated by variability in the amount of creatinine generated and its turnover as a function of muscle mass, age, diet, and concurrent illnesses and conditions as well as the inherent inaccuracy of collecting a timed (usually 24-hour) urine specimen (9). Variability in serum creatinine measurement has been improved with development and implementation of an isotope dilution mass spectrometry reference standard for creatinine measurement and reporting (14), although other laboratory and biologic variability remains.

Serum Creatinine–Based Estimating Equations

Given the difficulty with measuring and accurately knowing GFR, a variety of formulas have been derived to estimate either creatinine clearance, as a GFR surrogate, or GFR itself. Use of these estimating equations requires a number of assumptions about creatinine production and excretion, their relationship to age, sex, weight, and in some cases, race or ethnicity, and the presence of steady-state kidney function and serum creatinine concentration.

Probably the best known and most used until relatively recently is the simple Cockcroft–Gault formula for estimation of creatinine clearance (not GFR) (15) (Table 1). This formula was derived nearly 40 years ago from examination of 249 hospitalized men (all white) without known liver or kidney disease between the ages of 18 and 82 years old with mean serum creatinine values of 0.99–1.78 mg/dl. A 15% reduction in the calculated creatinine clearance in women to adjust for their lower creatinine generation per kilogram of body weight was proposed on the basis of the assumption that creatinine generation in women was 10%–20% less on a weight basis compared with men, but this figure was not derived from study of individual subjects. If it were not for its simplicity and continued use as the basis

Table 1. Cockcroft–Gault, Modification of Diet in Renal Disease, and CKD Epidemiology Collaboration GFR-estimating equations

Estimating Equation Name	Estimating Equation Formula
Cockcroft–Gault	$(140 - \text{age}) \times \text{weight} / 72 \times \text{SCr} \times 0.85$ (if a woman)
MDRD (four-variable)	$175 \times \text{SCr}^{-1.154} \times \text{age}^{-0.203} \times 0.742$ (if a woman) $\times 1.212$ (if black)
CKD-EPI (creatinine)	$141 \times \min(\text{SCr}/\kappa, 1)^\alpha \times \max(\text{SCr}/\kappa, 1)^{-1.209} \times 0.993^{\text{age}} \times 1.018$ (if a woman) $\times 1.159$ (if black), where κ is 0.7 for women and 0.9 for men, α is -0.329 for women and -0.411 for men, min indicates the minimum of SCr/κ or 1, and max indicates the maximum of SCr/κ or 1
CKD-EPI (cystatin)	$133 \times \min(\text{Scys}/0.8, 1)^{-0.499} \times \max(\text{Scys}/0.8, 1)^{-1.328} \times 0.996^{\text{age}} \times 0.932$ (if a woman), where min indicates the minimum of SCr/κ or 1, and max indicates the maximum of SCr/κ or 1
CKD-EPI (cystatin-creatinine)	$135 \times \min(\text{SCr}/\kappa, 1)^\alpha \times \max(\text{SCr}/\kappa, 1)^{-0.601} \times \min(\text{Scys}/0.8, 1)^{-0.375} \times \max(\text{Scys}/0.8, 1)^{-0.711} \times 0.995^{\text{age}} \times 0.969$ (if a woman) $\times 1.08$ (if black); where κ is 0.7 for women and 0.9 for men, α is -0.248 for women and -0.207 for men, min indicates the minimum of SCr/κ or 1, and max indicates the maximum of SCr/κ or 1

MDRD, Modification of Diet in Renal Disease; CKD-EPI, CKD Epidemiology Collaboration; SCr, serum creatinine; Scys, serum cystatin C.

of many medication dosing adjustments, this formula would likely have been relegated to the trash heap long ago, because it has generally been found to be the least accurate of commonly used prediction equations.

The Modification of Diet in Renal Disease Study and a New Era of GFR-Estimating Equations

A turning point in how clinicians assess GFR occurred in 1999, when Levey *et al.* (16) published a GFR-estimating equation derived from baseline data of subjects enrolled in the Modification of Diet in Renal Disease (MDRD) Study, a randomized trial that assessed effects of BP lowering and dietary protein restriction on progression of what we now call CKD (16). GFR was measured using renal clearance of ^{125}I -iothalamate in 1628 subjects and compared with creatinine clearance, urea clearance, the mean of these two clearances, the reciprocal of the serum creatinine concentration, the Cockcroft–Gault formula, a formula on the basis of creatinine, urea clearance, and race (black or not), and two regression equations using serum creatinine, age, sex, race (black or not), serum urea nitrogen (SUN) concentration, and either serum albumin concentration or urine urea nitrogen (UUN) concentration. The MDRD cohort was 60% men, 88% white, ages 18–70 years old (mean = 50.6 ± 12.7 years old) and included only 6% patients with diabetes, with an overall mean serum creatinine of 2.3 mg/dl, GFR of 39.8 ml/min per 1.73 m², and creatinine clearance of 48.6 ml/min per 1.73 m². Creatinine clearance and the Cockcroft–Gault equation systematically overestimated GFR, and urea clearance underestimated GFR, whereas the mean of the creatinine and urea nitrogen clearances was much more accurate than either. Even more accurate was a prediction equation using serum creatinine, demographic variables, SUN, and UUN. An equation with serum creatinine, demographic variables, SUN, and albumin was less accurate than the UUN-containing equation and also slightly less accurate than the creatinine clearance/urea clearance mean, but it was proposed as being the most practical for clinical use. A further simplified four-variable equation (including only serum creatinine, age, sex, and race [black or not]) (A.S. Levey *et al.*,

unpublished data) was modified on the basis of use of standardized serum creatinine assays (17) (Table 1) is now used by the majority of clinical chemistry laboratories in this country for eGFR reporting. The MDRD equation expresses GFR normalized for body surface area (BSA) in milliliters per minute per 1.73 m², whereas the Cockcroft–Gault formula and most clearance measurements are expressed as milliliters per minute. Whether BSA normalization of GFR is physiologically or clinically correct remains a matter of debate (18–22).

Although most clinical laboratories report eGFR using the modified four-variable equation, other equations, most notably the CKD Epidemiology Collaboration (CKD-EPI) equations (23), have been derived using serum creatinine, serum cystatin C (24), or both (1,24,25) (Table 1). Additional equations include the Lund–Malmö (26), Mayo Clinic (27), the Berlin Initiative Study (28), and the Chronic Renal Insufficiency Cohort (29) formulas, among others, some of which were developed for specific ethnic/racial groups, patient populations, or disease states (30,31). Cystatin C is a cysteine proteinase inhibitor produced by all nucleated cells. It is freely filtered across the glomerular filtration barrier, and then, it is virtually completely reabsorbed and catabolized in the proximal tubule. Plasma cystatin C concentrations have been shown to correlate with GFR. Some estimating equations using both serum creatinine and cystatin C seem to be more accurate than formulas using either alone (24,25).

The CKD-EPI equation, developed and validated through a collaborative effort with data from 26 research studies and clinical populations, provides eGFRs that are a bit higher than those calculated with the modified MDRD equation, with slightly less bias and slightly better accuracy (23). It is more accurate at eGFR ≥ 60 ml/min per 1.73 m², whereas the MDRD equation may be more accurate at lower levels of GFR (32,33). However, neither equation has a $P_{30} > 80\%$ in patients with eGFR < 60 ml/min per 1.73 m², in whom the interquartile (25th to 75th percentile) range of difference from measured GFR is approximately 12 ml/min per 1.73 m² (and twice that in patients with eGFR ≥ 60 ml/min per 1.73 m²). As I have said many times to my fellows, if measurement of serum sodium concentration had this degree of precision, we would stop measuring it.

Nonetheless, the CKD-EPI equation is now generally preferred over the MDRD equation because of, at least in part, its lower misclassification of patients with relatively well preserved kidney function as having CKD, although the performance of each varies depending on the population studied (34).

eGFRs from the MDRD and CKD-EPI equations using serum creatinine, cystatin C, and both have been extensively studied as tools to assess relative risks in populations of diverse patients with CKD for clinically important outcomes, including AKI, complications of CKD, development of ESRD, cardiovascular morbidity, and all-cause and cardiovascular mortality (2). What has not been as well studied is how to best know the actual GFR in individual patients, such as the patient presented here, with rather advanced CKD who may (or may not) have symptoms consistent with uremia and may (or may not) benefit from starting dialysis without resorting to inulin or other exogenous substance-based clearances. In fact, in the only prospective, randomized, controlled trial evaluating the timing of starting dialysis, GFR was estimated with the Cockcroft–Gault equation (35). There are also potentially important differences in assessment of CKD progression on the basis of slopes of eGFR compared with measured GFR (36–38).

A recent report from the Swedish Renal Registry CKD (SRR-CKD) compared measured GFR using iothalamate plasma clearance with eGFRs derived from the Lund–Malmö, CKD-EPI, Mayo, MDRD, and Cockcroft–Gault equations (39). Because patients were from clinics in Sweden, the sample was demographically very different from my patient and many others in the United States. Because the MDRD and CKD-EPI equations are most commonly used in the United States, only results with these equations will be reviewed here. For patients with measured GFR=11–20 ml/min per 1.73 m², the median bias values were 1.3 and 1.8 ml/min per 1.73 m² (9.4% and 12.9%) for the CKD-EPI and MDRD equations, respectively. For patients with measured GFR ≤10 ml/min per 1.73 m², the median bias values were 1.2 and 1.7 ml/min per 1.73 m² (13.2% and 19.3%) for the CKD-EPI and MDRD equations, respectively, indicating slight systematic overestimation of GFR. The accuracy of these equations in absolute terms (milliliters per minute per 1.73 m² difference between eGFR and measured GFR) was modest, with as many as 20% of patients with measured GFR ≤10 ml/min per 1.73 m² having a difference >5 ml/min per 1.73 m² and as many as 6.5% of patients having a difference >10 ml/min per 1.73 m². For patients with measured GFR of 11–20 ml/min per 1.73 m², nearly one third of patients had a difference >5 ml/min per 1.73 m², and about 10% had a difference >10 ml/min per 1.73 m².

Additional information is available from the MDRD and CKD-EPI datasets (23). There were 141 and 144 patients with eGFR<15 ml/min per 1.73 m² in the MDRD and CKD-EPI validation cohorts, respectively. In both cohorts, 25% of subjects with eGFR<15 ml/min per 1.73 m² had measured GFR values >15 ml/min per 1.73 m². Most of these were in the 15–29 ml/min per 1.73 m² range, but two patients had measured GFR values in the 60–89 ml/min per 1.73 m² range (Figure 1). In practical terms, this means that one of four patients urged by their nephrologists to accept a kidney transplant or start dialysis when eGFR falls below 15 ml/min per 1.73 m² will, in fact, have a measured GFR above and in some patients much above, this range.

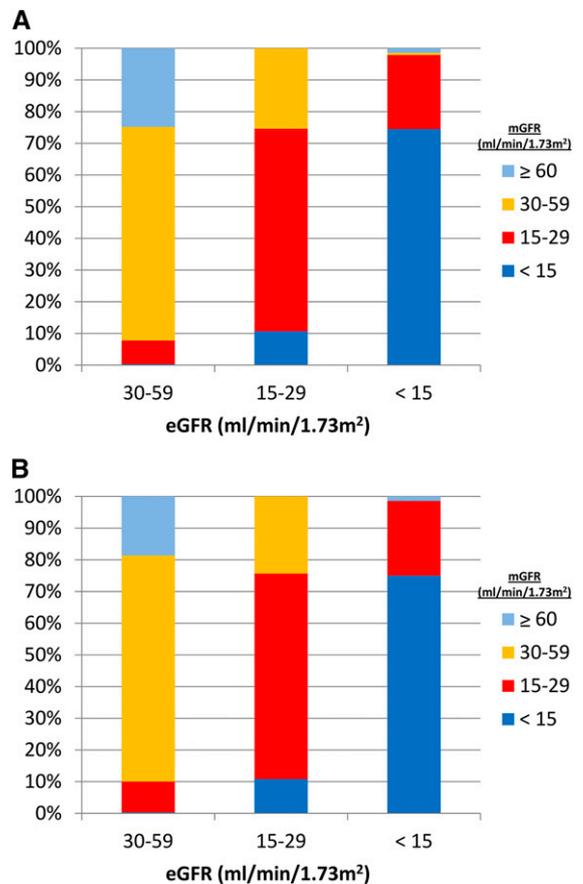


Figure 1. | Significant differences exist between mGFR and eGFR with both the MDRD and CKD Epidemiology Collaborative equations. Comparison of eGFR using (A) the MDRD and (B) the CKD Epidemiology Collaboration equations compared with mGFR (iothalamate). MDRD, Modification of Diet in Renal Disease; mGFR, measured GFR. Reference 23.

Several other studies have similarly addressed comparisons between eGFR and measured GFR with advanced CKD (GFR<15 ml/min per 1.73 m²), most using inulin or radioisotope clearances. Each of these studies corroborates findings of the SRR-CKD Study; regardless of the population statistics on bias and accuracy, some patients with eGFR around 10 ml/min per 1.73 m² will have measured GFR values of 20 ml/min per 1.73 m² or higher, and some will have measured GFR values near 5 ml/min per 1.73 m² (40–47). Few if any blacks were included in any of these reports, with the exception of a report from the African-American Study of Hypertension and Kidney Disease Trial, which included derivation of its own formula for eGFR calculation in blacks (48). A recent report identified differences in eGFR and CKD staging on the basis of genetic determinants of the proportion of African ancestry in self-reported blacks and Hispanic/Latino Americans, further confounding GFR assessments in these populations (49).

A quote from Soveri *et al.* (7) from the SRR-CKD Study cited above is worth considering:

Although our results compared well with others, the Acc30 (percent of estimated within 30% of measured) is still strikingly bad on an individual basis. Even when

using the best possible equation, almost 24% of the individuals with an eGFR of 10 ml/min/1.73 m² will have true GFR values of <5 or >15 ml/min/1.73 m². Thus, our results stress the importance not to make important decisions regarding the timing of dialysis initiation or timing of vascular access surgery based on eGFRs. In fact, for patients with higher age and diabetic nephropathy, there is even greater overestimation of true GFR and worse accuracy (7).

Summary

Returning to my patient, the MDRD eGFR was 11 ml/min per 1.73 m², and the CKD-EPI eGFR was 10 ml/min per 1.73 m². Calculated BSA values ranged from 1.80 to 1.91 m² depending the formula used, leading to an eGFR of 11.4–12.1 ml/min not normalized to BSA. Twenty-four hour urinary creatinine and urea nitrogen clearances were 16.8 and 10.3 ml/min, respectively (mean=13.6 ml/min). We discussed starting dialysis (she was interested in doing peritoneal dialysis), but because her symptoms improved spontaneously over a few weeks and she was without significant metabolic or laboratory complications of CKD, we together opted for a watch and wait approach before placing a peritoneal dialysis catheter.

Conclusions

GFR-estimating equations have clearly been a major advance in detection of patients with CKD and the epidemiologic study of CKD and its outcomes, although concerns remain about their imperfections and risk of misdiagnosis (50–53). However, they are just estimating equations; clinicians who use them should be familiar with their strengths and weaknesses and understand their potential for significant inaccuracy. Perhaps new methods for determining GFR will eventually make their way into clinical practice (54–56).

Precise knowledge of GFR might be of value in patients, such as mine, who may have symptoms suggestive of uremia given that symptoms of uremia can be subtle and are non-specific, medication dosing (or avoidance) (57–59), use of contrast media, assessing individuals considering living kidney donation (60–62) or who are transplant recipients (63), and planning timing of dialysis access or the start of dialysis and transplantation. Knowing the measured GFR might be important also when trying to assess kidney function in patients who are elderly (64), are morbidly obese, have significant nonrenal acute or chronic illness, have reduced muscle mass, have liver disease, have malnutrition, or had an amputation. Available estimating equations do not have verified accuracy in various non-United States and European white and black racial/ethnic groups (30) or those at extremes of muscle mass or body size or who consume vegetarian or vegan diets. We still have much to learn about relationships between BMI, muscle mass, and creatinine excretion (21,65,66). Furthermore, the serum creatinine concentration on which these formulas are based may be influenced by diet, creatine supplements, and certain medications (*i.e.*, trimethoprim and cimetidine). Cystatin C may be influenced by thyroid function, adiposity, inflammation, and other factors (67).

Although I have focused, given the patient presented, on low levels of GFR and stage 5 CKD, the accuracy of GFR-estimating equations is much worse at higher GFR levels (Figure 2), although better for the CKD-EPI compared with MDRD equation (32). As such, nephrologists should probably arrange to have more accurate means of measuring GFR available when needed until more consistently accurate estimating equations become available, which has also been suggested by others (68). Averaging the urea nitrogen and creatinine clearances may be helpful but is, by no means, ideal. Decisions regarding starting dialysis can be complex and must take into consideration not just GFR estimates but also, careful review of patient symptoms and other laboratory data. As should be clear from the above discussion, using an isolated eGFR as a trigger for starting dialysis is overly simplistic and likely to often lead to erroneous clinical decision-making.

One final thought—perhaps clinical laboratories could report not just calculated eGFR but also, a 95% confidence interval, interquartile (25th to 75th percentile) range, other indicator of the range of potential actual GFR levels that the eGFR might represent, or even some simple explanatory text, which is now often done when laboratories report lipid panel results. This might help clinicians to better appreciate the range of potential actual measured GFRs around a reported eGFR in their patients when a difference between 10 and 30 ml/min per 1.73 m² is clinically important.

Questions

Jordana Cohen, MD (Research Fellow)

In the patient who you presented, if an inulin clearance showed a measured GFR of 5 ml/min per 1.73 m², would

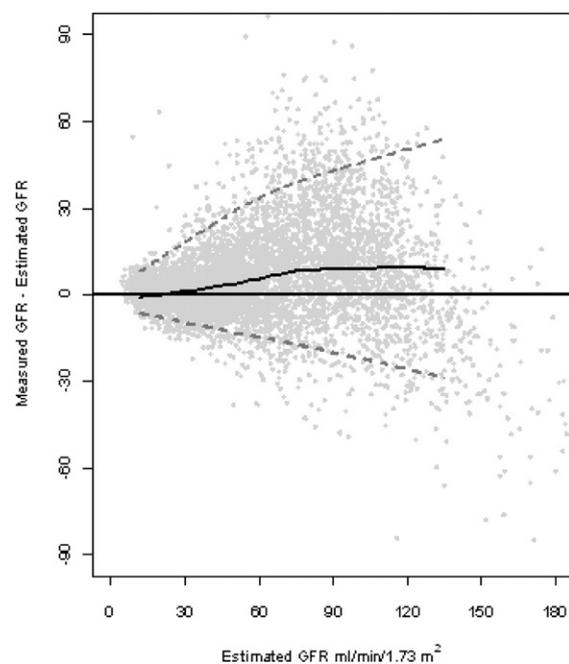


Figure 2. | Difference between mGFR and eGFR (MDRD equation) from the combined dataset derived from 10 studies. mGFR, measured GFR; MDRD, Modification of Diet in Renal Disease. Reprinted from reference 47, with permission.

that change your management decision given that she is now asymptomatic with no metabolic derangements?

Answer

In essence, the issue here is how low can you go, whether using measured GFR or eGFR, in waiting to start dialysis in an asymptomatic or minimally symptomatic patient. Although the target for late-start dialysis in the only prospective, randomized clinical trial of early- versus late-start dialysis, the Initiating Dialysis Early and Late (IDEAL) Study, was eGFR of 5.0–7.0 ml/min, most patients started with eGFR > 7.0 ml/min because of symptoms or other indications (35); therefore, this study was not able to directly answer this question. Several retrospective studies suggest that dialysis initiation with eGFR < 5 ml/min per 1.73 m² is associated with lower mortality than higher eGFR dialysis starts (69–72), although such studies are limited by survival bias, confounding by indication, and other issues. At least one prospective cohort study, however, found a significantly higher mortality (hazard ratio, 4.65; 95% confidence interval, 2.28–9.49) among patients not yet on dialysis with eGFR < 7.5 ml/min per 1.73 m² (73). A recent Canadian clinical practice guideline recommends deferring dialysis until the eGFR is 6 ml/min per 1.73 m² (74), whereas another indicates that clinical indications for starting dialysis “often but not invariably” occur when eGFR is 5–10 ml/min per 1.73 m² (2). Although seemingly safe in the absence of symptoms or other indications for dialysis, such late starts necessitate close patient follow-up.

Jamie Lin, MD (Nephrology Fellow)

Knowing that these equations are by no means perfect in estimating renal function, are there any studies that assess whether certain comorbidities should influence dialysis initiation timing?

Answer

Diabetes and cardiovascular disease are often cited as indicators for earlier start of RRT and are more common in patients who start dialysis at higher eGFR levels (69). In the IDEAL Trial, however, age, diabetes, BMI, history of cardiovascular disease, and serum albumin concentration did not significantly influence the primary study finding of no benefit of a planned dialysis start at the higher eGFR level (35).

Rebecca Seshasai, MD (Research Fellow)

Why do we still dose medications on the basis of the Cockcroft–Gault estimation of creatinine clearance when better estimating equations are now available?

Answer

Use of the Cockcroft–Gault formula was recommended by the US Food and Drug Administration (FDA) in 1998, long before other GFR-estimating equations were available. Stevens *et al.* (59) compared measured GFR with eGFR using the MDRD equation and the Cockcroft–Gault equation. Discordance in FDA-assigned kidney function categories was found in 22%–34% of comparisons and recommended drug dosages in 12%–18% of comparisons, with 82%–89% concordance between the estimating equations. Of note is that eGFR in this analysis was adjusted to

remove BSA normalization, something that is not typically considered in practice but is probably appropriate for this use (75). There also seems to be substantial drug-dosing discordance in older individuals comparing MDRD and CKD-EPI equations (76). It is not clear which formula is superior in terms of maximizing drug efficacy and minimizing drug toxicity (58,75).

Disclosures

J.S.B. is the President of the National Kidney Foundation.

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