Utilizing Longitudinal Within-Individual Changes of Serum Creatinine, Cystatin C, and/or eGFR to Optimize Clinical Sensitivity and Eliminate Race and Gender Corrections

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The recent recommendation by the American Society of Nephrology/National Kidney Foundation task force to immediately eliminate the “race” factor in the estimated glomerular filtration rate (eGFR) equation (1) is a much-needed and long-overdue correction of the original Modification of Diet in Renal Disease (MDRD) and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) eGFR equations. While the primary and continual goal of the MDRD, CKD-EPI, and other eGFR equations has been to agree with measured GFR (mGFR), we believe this was misguided as shown by the necessity of updating to the CKD-EPI (2021) equation to improve its clinical ability to detect and monitor changes in kidney function for all persons. This new emphasis will enhance the role of the eGFR as a clinical guide for determining chronic kidney disease (CKD) stage and possible referral to nephrology. Because eGFR is calculated from serum creatinine (sCr) and/or cystatin C (sCysC), which are reliable measurements, we propose that these measurements and eGFRs calculated from them are actually more clinically useful, more reliable, and far more used than mGFRs, which have much greater analytical and physiological variation (2–5).

Indeed, it was the variability of the mGFR, not the more reliable sCr, that required both the MDRD and CKD-EPI equations to accept wide error tolerances of ±30%, with 81% of the MDRD eGFRs and 84% of CKD-EPI eGFRs within the 30% error tolerance.

Several studies have shown both physiologic and methodologic variation with mGFRs. Seegmiller et al. (3) showed a mean bias of −15% (95% CI −35% to +7%) between iohexol and iothalamate mGFRs and a mean bias of +36% (95% CI +13% to +91%) between iohexol and creatinine clearance mGFRs. Ocampo et al. (4) concluded that mGFRs by different methods showed wide variations compared to inulin clearance. For example, the mean bias between creatinine clearance and inulin GFR was only 0.4 mL/min/1.73 m², the variation ranged from −15 to +21 (95% CI). While the mean bias between creatinine clearance and inulin GFR was only 0.4 mL/min/1.73 m², the variation

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ranged from −22 to +22 mL/min/1.73 m². Another study clearly showed that mean within-individual changes of both sCr (5.8%) and sCysC (5.4%) were much more stable over a 6-month period than mGFR by creatinine clearance (18.7%) (5).

The addition of factors for race in the MDRD/CKD-EPI equations was apparently not based on sound data. Grubbs (6) noted that use of race corrections in these equations was based on weak assumptions from 3 small, mostly irrelevant studies, which were the basis for concluding that Black persons had more muscle mass, although muscle mass was not measured. In addition to abandoning race-based “correction” factors, we propose a simple approach to further improve interpretations of results for sCr, sCysC, and eGFR. We believe there should be no further efforts to “improve” eGFR equations by mathematical manipulations to achieve better agreement with mGFRs, which are imprecise, more expensive, and impractical for routine or urgent situations.

Our proposed approach has abundant support in the literature and is based on establishing a person’s baseline sCr and/or sCysC concentrations, followed with appropriate serial monitoring of clinically relevant within-individual changes. Thus, each person’s baseline values would obviate the need for correction factors based on race, sex, and possibly age. This concept is similar to the long-standing use of within-individual changes in serum creatinine to guide detection and monitoring of acute kidney injury, as noted in a recent report (7). By virtually eliminating the need for correction factors based on race, nationality, or sex differences in sCr, sCysC, and eGFR calculations, our proposal builds on the NKF/ASN recommendations and allows earlier detection of declining kidney function, even while sCr, sCysC, and eGFRs remain within their reference intervals.

Our laboratory community must also correct the erroneous perceptions that changes in sCr concentrations do not detect early-stages of CKD and that large decreases in mGFR are associated with insignificant changes in sCr in the so-called creatinine-blind range of early kidney impairment. This idea originates from an often-referenced 1985 study by Shemesh et al. that highlighted a zone in which sCr remained “normal” as mGFR decreased (8). Unfortunately, this has been widely cited as fact. While that study (8) was an excellent work on the physiology of creatinine handling by kidney tubules, the authors’ clinical conclusion was based more on physiology than clinical study. In fact, their Table 3 shows that serum creatinine increased from 1.4 to 2.3 mg/dL as inulin clearance mGFR decreased from 61 to 32 mL/min/1.73 m² in glomerulopathic patients. Their conclusion that “serum creatinine in glomerulopathic patients is unlikely to become elevated overtly until GFR has fallen by at least 50%” is not supported by several large studies showing the clinical significance of seemingly small changes in creatinine that signaled increased mortality and morbidity.

Onuigbo and Agbasi concluded that following within-individual trajectories of a patient’s sCr is a most useful diagnostic tool, both for short- and long-term management of patients, and illustrated this with cases from a variety of patients with acute kidney injury and/or CKD (9). Seemingly small changes in serum creatinine allowed earlier identification of patients with milder kidney impairment, thus allowing general clinicians to detect earlier stages of kidney impairment, independent of variables such as age, sex, race, or nationality.

In a prospective study of over 5000 patients undergoing cardiac surgery, Shavit et al. found that the risk for in-hospital mortality increased progressively with every 0.2 mg/dL (18 μmol/L) increase in preoperative sCr, even for changes within the “normal” range (10). As examples, the mortality rate went from 2.8% (preoperative sCr ≤1.0 mg/dL) to 4.6% (sCr 1.10–1.20 mg/dL) to 7.4% (sCr 1.21–1.40 mg/dL, etc.). They noted significant increases in mortality with every 15 mL/min/1.73 m² decrease in eGFR (CKD-EPI or the MDRD),
suggesting that changes in eGFR could also be followed.

In a study highly relevant to racial issues, Bahvsar et al. followed over 800 African Americans with hypertensive CKD for a mean follow-up of 103 months, comparing the usefulness of mGFR, sCr, eGFR, sCysC, and β-trace protein (BTP) concentrations to predict end-stage renal disease (ESRD) (11). For the 246 participants who reached ESRD during follow-up, they found that higher concentrations of each marker were strongly and significantly associated with higher risk of ESRD, with both sCysC and BTP better at predicting ESRD.

Jhee et al. showed the importance of sCr concentrations in the middle to upper reference interval and identified 9000 subjects at baseline without underlying kidney disease and with both CKD-EPI eGFR > 60 mL/min and sCr in normal to high-normal concentrations (12). During mean follow-up of 8.4 years, the odds of progression to eGFR < 60 mL/min increased as sCr increased, even while sCr remained within the reference interval. These findings show that kidney injury is detectable in its early stages by following each person’s sCr even while still within reference intervals, and is not simply a consequence of starting with higher sCr.

Kim et al. evaluated over 1300 patients in stages 3 to 5 CKD (eGFR <60 mL/min/1.73 m²), of whom 134 patients progressed to ESRD, requiring either dialysis or kidney transplant (13). They concluded that slope of eGFR calculated from both sCr and sCysC were equivalent in predicting progressing to ESRD in patients in CKD stages 3 to 5.

Spanaus et al. followed changes of sCr, cysC, BTP, and mGFR by iohexol clearance during progression of CKD in 177 patients with primary non-diabetic CKD for periods of 3 to 84 months (median 53 months) (14). They noted that the concentrations of all 3 markers increased progressively with decreasing mGFR, and their diagnostic performance for detecting even minor decreases in kidney function were similar, although BTP was slightly better. They also noted the absence of a “creatinine-blind range” erroneously concluded earlier (8), because creatinine, even within the reference interval, increased in the early stages of declining kidney function as detected by iohexol GFR. They concluded that each serum biomarker, including sCr, strongly correlated with mGFR, and that each was useful for diagnosing early changes in kidney function as mGFR decreased from >120 to < 60 mL/min/1.73 m².

Dalton concluded that Shemesh et al. (8) misinterpreted their data as indicating sCr did not increase until mGFR had fallen by 50%. Dalton cited the Spanaus report as unequivocal evidence that “longitudinal monitoring of serum creatinine in any individual will ensure early detection of GFR decline and incipient renal disease” (15).

Interpreting within-individual changes in longitudinal sCr will require awareness of factors not related to kidney function that can affect sCr, such as diet (boiled red meat), fluid restriction, drugs (trimethoprim, cimetidine, famotidine, etc.), and significant changes in lifestyle that affect muscle mass, including hormonal therapy, sex changes, kidney donation, and amputation.

**FUTURE NEEDS**

**Develop Baseline Serum Creatinine/eGFR Concentrations**

As with monitoring cholesterol, glucose/HbA1c, and other tests, general clinicians should be encouraged to obtain steady-state sCr/eGFR in normally hydrated (nonfasting) outpatients. In many patients, historical sCr data would already be available to determine a patient’s baseline. Because increased testing for baseline sCr will increase initial costs, the benefits of earlier detection of CKD will have to be evaluated, including minimizing socioeconomic disparities and...
reducing the annual $120 billion Medicare and Medicaid costs of CKD and ESRD.

**Improve Precision of Serum Creatinine Methods**

A high level of precision must be a goal for all sCr methods, equally important as and likely more difficult than, isotope dilution mass spectrometry standardization among sCr methods. A suggested goal could be for 90% of duplicate measurements on patient samples to agree within 0.05 mg/dL (4.4 μmol/L) for creatinine concentrations up to 2 mg/dL (176 μmol/L) (16).

**Develop Criteria for Interpreting Within-Individual Changes in sCr/eGFR/sCysC That Warrant Investigation and Possible Referral to Nephrology**

Relevant criteria could be an increase in sCr of 0.20 mg/dL (17 μmol/L) or a percentage change of 20% for higher sCr. This is in synchrony with new recommendations for creatinine changes in acute kidney injury of 0.20 mg/dL for baseline sCr <1.00 mg/dL (88 μmol/L) or changes of +20% from baseline for sCr >1.00 mg/dL. (7). Importantly, appropriate time intervals need to be developed over which to gauge these changes, perhaps at 3, 6, and 12 months.

While appropriate population reference intervals are always helpful, establishing a reliable personal baseline essentially creates a “unique” individual reference interval for that person, with changes in sCr, sCysC, and/or eGFR becoming the important parameter.

**Report Creatinine in Units That Make Changes More Apparent**

Similar to the recommendation to report high-sensitivity troponin results in ng/L, reporting creatinine results in units of either mg/dL to 2 decimal places, mg/L, or μmol/L would make clinical and analytical changes more apparent. Thus, changes from 62 to 79 μmol/L or 7.0 to 9.0 mg/L would appear more significant than a change from 0.7 to 0.9 mg/dL.

**Nonstandard Abbreviations:** eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CKD, chronic kidney disease; mGFR, measured glomerular filtration rate; sCr, serum/plasma creatinine; sCysC, serum/plasma cystatin C; BTP, beta trace protein; ESRD, end-stage renal disease.

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