Cystatin C Is More than GFR, and This May Be a Good Thing

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For measuring GFR, an exogenous marker is injected into the patient with timed marker levels assayed in the urine and plasma (urinary clearance) or plasma alone (plasma clearance). The essential properties of the exogenous marker are that it is metabolically inert and cleared exclusively by glomerular filtration, but cost, time, and discomfort make measured GFR impractical in most clinical settings. Instead, endogenous markers have been widely used. Unlike exogenous markers, non-GFR determinants of endogenous markers exist but are sometimes difficult to interpret.

Estimated GFR (eGFR) based on serum creatinine (eGFRcCr) uses age, gender, and race in the estimating equation to model the non-GFR determinants of serum creatinine (largely muscle mass). However, these demographics do not fully account for non-GFR determinants of creatinine. In particular, GFR is higher at the same serum creatinine level in healthy individuals with higher muscle mass than those with chronic kidney disease (CKD) and lower muscle mass. Cystatin C is another endogenous marker cleared by filtration, and its serum levels are more highly correlated with GFR than serum creatinine. The non-GFR determinants of cystatin C are less defined and more curious; cystatin C is a 14-kD protease inhibitor with anti-atherosclerotic activity in animal models and is a strong predictor of mortality or cardiovascular disease (CVD) among individuals with normal eGFRcCysC or CKD.

In this issue of JASN, Mathisen et al. provide novel insight into the non-GFR determinants of both serum creatinine and cystatin C. They found that higher serum creatinine levels or lower eGFRcCr had a residual association with higher diastolic BP, not smoking, and increased physical activity. Nonsmokers and physically active individuals may be expected to have higher muscle mass, resulting in higher serum creatinine levels, potentially explaining this association. They also found that higher cystatin C levels or lower eGFRcCysC had a residual association with being a smoker, decreased physical activity, higher triglycerides, higher LDL cholesterol, lower HDL cholesterol, and obesity. This residual association with smoking and obesity has been previously reported, but previous studies adjusted for urinary creatinine clearance instead of measured GFR (mGFR). Mathisen et al. also found increased Framingham risk scores with lower eGFRcCysC but not with lower mGFR or lower eGFRcCr. These findings argue that eGFRcCysC is a better predictor of CVD than GFR because the non-GFR determinants of cystatin C, possibly its anti-atherosclerotic activity, also reflect cardiovascular risk.

One potential objection to their conclusion is that eGFR may have a residual association with cardiovascular risk factors because mGFR is imprecise. In other words, could eGFR capture a residual association that reflects the true GFR signal missed as a result of error with mGFR? The study by Mathisen et al. suggests this hypothesis is unlikely. The residual associations with eGFRcCr were different and sometimes in the opposite direction of residual associations with eGFRcCysC. If residual associations with eGFR could be fully explained by imprecision of mGFR, then residual associations with eGFRcCr should be similar to residual associations with eGFRcCysC. Furthermore, a sensitivity analysis was performed assuming 30% of the variance in direct GFR measurement was error, but the residual associations with eGFR remained.

How should these findings influence clinical practice? A new cystatin C equation that uses obesity, smoking, and serum lipids to improve the estimation of GFR could be developed. However, such an equation would have substantial drawbacks. Obesity, smoking, and lipids are only correlates of the non-GFR determinants of cystatin C and do not fully capture all of the non-GFR determinants of cystatin C. Incorporating the variables obesity, smoking, and lipids into a new eGFRcCysC may lead to a more accurate estimate of GFR, but, paradoxically, the new eGFRcCysC would be less predictive of CVD than cystatin C alone. In particular, individuals who are obese, smoke, or have dyslipidemia would have their eGFR increased by the new cys-
tatin C equation. In fact, by controlling for these cardiovascular risk factors, the new eGFRcysC may be less predictive of CVD than GFR! Indeed, the variables used to model non-GFR determinants of a marker fundamentally influences how eGFR predicts outcomes. For example, the use of age to model the non-GFR determinants of serum creatinine inflates mortality risk estimates with eGFRcys because age itself is a potent predictor of mortality.14

The study by Mathisen et al.,13 has a few limitations worth noting. Patients who reported renal disease, diabetes, or CVD were excluded. Similar studies of less select samples are needed. All analyses were adjusted for age and gender. However, the residual associations between eGFR and cardiovascular risk factors with adjustment only for mGFR should have been provided for three reasons. First, age and gender are variables used to calculate eGFRcys. Second, age and gender may correlate with the non-GFR determinants of cystatin C. Third, there has been no adjustment for age and gender with the use of eGFR to define CKD.

Given this residual association of cardiovascular risk factors with cystatin C levels, it might seem that cystatin C should not be used as a kidney function test. Perhaps the focus with cystatin C should be to improve prediction of clinical outcomes instead of optimizing the estimation of GFR. To the extent that cystatin C helps identify patients at higher risk for kidney failure, mortality, and CVD not detected by serum creatinine, it is useful. If the incremental improvement in risk prediction with cystatin C is due in part to its non-GFR determinants, then one might argue that cystatin C is not a pure kidney marker. However, much of the variation in GFR itself is not due to parenchymal injury in the kidney. Indeed, there is no association between mGFR and nephrosclerosis on renal biopsy among normal adults after controlling for age.16 Variation in GFR can be due to nonrenal causes such as dietary protein intake, volume status, hemodynamics, or even the indexing of GFR to body surface area.17

Perhaps the most useful application of cystatin C is as a confirmatory test for individuals with an eGFRcys <60 ml/min per 1.73 m², where cystatin C identifies the subset with nearly all of the increased risk for kidney failure, cardiovascular events, and mortality.18 If cystatin C can find high-risk patients for whom targeted management is beneficial, then it is clinically useful. This should be the focus instead of a more exact GFR estimate.

REFERENCES

Hepatic hydroxymethyl glutaryl–CoA reductase inhibitors, known as statins, are among the most commonly prescribed drugs in the world. Scientists studying microorganism host defense first identified statins in the 1970s. They were eventually shown in large randomized trials, such as the Scandinavian Simvastatin Survival Study and the West of Scotland Coronary Prevention Study, to confer substantial clinical benefits over placebo in individuals with hypercholesterolemia. Statins are now a cornerstone for both primary and secondary prevention of coronary heart disease. A number of noncardiovascular benefits—such as in dementia, sepsis, and cancer—have also been proposed, largely on the basis of observational data.

In this issue of JASN, Molnar et al. report the results of an observational study on the association between statin use and decreased incidence of perioperative acute kidney injury (AKI) and mortality. The population-based cohort contained data on 213,347 Ontario Drug Benefits Plan recipients who were aged ≥66 years and underwent elective cardiac, thoracic, vascular, abdominal, or retroperitoneal surgery between 1995 and 2008. As anticipated, those who received statins tended to have more comorbid atherosclerotic disease, hypertension, diabetes, and congestive heart failure; to be treated with a greater number of total and cardiovascular-related medications; to have undergone more extensive cardiovascular diagnostic evaluations and procedures; and more likely to be undergoing cardiac and vascular surgery. On this basis, unadjusted analyses demonstrated an increased risk in perioperative AKI and dialysis use among statin users. However, upon multivariable and propensity score adjustment, statin use was associated with a 14 to 17% reduction in these outcomes. Curiously, unadjusted mortality was 27% lower in the statin group despite greater comorbid disease burden; mortality risk remained 15 to 21% lower after statistical adjustment. Analyses that appropriately accounted for healthier adherer bias and dose-response trends yielded corroborative findings. The population-based cohort design promotes generalizability, although, in fairness, only to elderly patients undergoing elective surgery.

As with all research on humans, internal validity of findings is contingent on accurate characterization of events and conditions. Absent available laboratory data, AKI was characterized solely on the basis of diagnostic codes. Considering the cohort’s era, the majority of hospitalizations would have been coded using the International Classification of Diseases, Ninth Revision classification system, which has only 28.3% sensitivity for AKI. Moreover, chronic kidney disease (CKD)—arguably the most important covariate—was assessed with only 22.9% sensitivity and 87.5% specificity (Appendix D-2). Thus, both the outcome and a critical covariate had substantial error rates.

An often-repeated mantra in epidemiologic research is that nondifferential misclassification biases toward the null hypothesis. In other words, if information on AKI or CKD or other covariates were inaccurate but randomly so, then a study would tend to find no association even if an association existed and would therefore not account for the protective association seen in this study. However, this is an oversimplification for at least two reasons. First, if errors in diagnostic codes were correlated—that is, errors in AKI codes were more common in those with errors in CKD codes, such as might occur for patients with limited medical follow-up—then measures of association could be biased in either direction. Second, we previously showed that AKI diagnostic codes in fact suffer from relevant nondifferential misclassification: codes have higher sensitivity in men than in women, in the elderly, and in those who die in-hospital. To the extent that statin use in the Ontario cohort differed by race, gender, and mortality, misclassification bias cannot be ignored.

As with any observational study, the potential for causal inference must also be interpreted in light of the underlying biological basis and literature precedent. Studies of animal models demonstrated that statin use is associated with a decreased risk for ischemia–reperfusion kidney injury. Proposed mechanisms include favorable effects on oxidative metabolism involving heme oxygenase 1, NF-κB, activator protein 1, metalonate, and nitric oxide. However, animal data do not invariably translate to clinical practice. For example, N-acetyl cysteine showed similar promise in preclinical models yet demonstrated little to no clinical efficacy in preventing perioperative AKI.

In addition, any cogent attempt to rationalize the study’s findings as causal should account for the graded trend toward incrementally better outcomes among patients exposed to statins for shorter periods (adjusted odds ratios 0.86, 0.77, and 0.61 for statin use >90, 30 to 90, and <30 days, respectively).