Cystatin C: A Marker of Renal Function or Something More?

Over the past decade, we have come to appreciate that individuals with even moderately reduced renal function are at increased risk for cardiovascular morbidity and mortality. There is no consensus, however, on how renal function should be measured. The most precise and accurate methods (such as inulin clearance) are impractical in the clinical setting and for larger research studies. Serum creatinine has been the mainstay by which renal function has been estimated for decades, but it is crude and can often be misleading. Age, weight, sex, and race influence creatinine production and thus need to be taken into account when evaluating a serum creatinine value. For example, an elderly woman with a serum creatinine in the “normal” range can have severely reduced renal function. Although measurements of serum creatinine are relatively inexpensive and widely available, they do have limitations.

In an attempt to address some of these limitations, equations have been derived to estimate either creatinine clearance or the glomerular filtration rate (GFR). The most commonly used equation for estimating creatinine clearance is the Cockcroft-Gault formula (1). GFR calculated by this equation correlates well with measured GFR when renal function is within the reference interval, but as renal function declines, it overestimates GFR because creatinine is removed not only by glomerular filtration but also by renal tubular secretion. When GFR is low, tubular secretion becomes an important factor. Another formula, the MDRD (Modification of Diet in Renal Disease) equation, is the most widely used to estimate GFR (2). It too has several limitations, including lack of validation within the reference interval, the susceptibility of the alkaline-picomole creatinine method to interferences, and the lack of harmonization of creatinine assays. The variation between laboratories for plasma creatinine may be 30% or more. This has serious implications when using an estimating equation that was derived with a different creatinine method (3).

The difficulty with estimating renal function by use of creatinine-based equations has led to a search for other markers of renal function. Cystatin C has been proposed to be such a marker because it purportedly is produced by all nucleated cells at a constant rate, is filtered at the glomerulus, and is taken up and degraded by the proximal tubular cells of the kidney. Unfortunately, despite the early enthusiasm, cystatin C is at best only a slightly better predictor and discriminator than creatinine (4). There may be several reasons for the lack of clear superiority over creatinine. For example, other factors are associated with and likely affect the cystatin C concentration, including age, weight, smoking, gender, and C-reactive protein (CRP) (4, 5). In addition, the cystatin C concentration may be affected by other conditions such as liver disease (6) and thyroid disease (hypo- or hyperthyroidism) (7, 8). Its utility in specific subgroups of patients, such as children, those with type I (9) or type II (10) diabetes mellitus, renal transplant recipients, the elderly (11), the obese, or those not in a steady state (e.g., acute renal failure), remains uncertain. The higher cost of cystatin C and the lack of ready availability have prevented its wide acceptance as the replacement for creatinine to estimate renal function.

Nonetheless, cystatin C may still be a marker with prognostic importance. Cystatin C is also a marker of inflammation, and like many other markers of inflammation, its plasma concentration may be higher in patients with decreased renal clearance. There is mounting evidence, however, that cystatin C may be a predictor of adverse outcomes independent of renal function. In this issue of Clinical Chemistry, Koenig et al. (12) examined the association between plasma cystatin C and risk for secondary cardiovascular events. They followed for nearly 3 years a cohort of 1033 individuals 30–70 years of age who had a history of coronary heart disease. The primary outcome was a combined endpoint of fatal and nonfatal cardiovascular events (myocardial infarction, cerebrovascular accidents, transient ischemic attacks, or death attributable to cardiovascular disease). During follow-up, 71 (6.9%) of the study participants experienced an event. Cystatin C and estimated creatinine clearance were not significantly associated with risk of a cardiovascular event. In contrast, higher plasma cystatin C was associated with an increased risk, even after adjusting for well-known risk factors, including CRP. Compared with individuals in the lowest quintile of cystatin C, those in the highest quintile had a more than a twofold increase in risk, even after adjusting for estimated creatinine clearance.

What are potential explanations for the observations of Koenig et al. (12)? One possibility is that cystatin C is a novel risk factor for cardiovascular events. A previous study from the PREVEND investigators in The Netherlands suggested that higher cystatin C concentrations increase the overall risk of death (13). Higher cystatin C was also associated with higher mortality in patients with acute coronary syndromes (14). The Cardiovascular Health Study of individuals 65 years and older found that higher cystatin C was associated with an increased risk of total mortality (15) and new-onset congestive heart failure (16). By contrast, a small nested case-control study in the Physicians’ Health Study found no association between cystatin C concentrations and risk of developing systemic atherosclerosis (17). In unadjusted models, higher concentrations have been associated with the degree of endothelial damage in women with preeclampsia, a condition also believed to be attributable to endothelial damage (18).

Cystatin C is considered an inflammatory marker, but its association with adverse outcomes in the study by Koenig et al. (12) was independent of CRP and other factors known to influence cystatin C concentrations. One note of caution is that the authors did not specify whether CRP and creatinine clearance were included as continuous or categorical variables; if the latter, there is still the potential for residual confounding.
Another possibility is that cystatin C is simply a better marker of reduced renal function than is creatinine. Several large studies have demonstrated that the risks of death, cardiovascular disease events, and hospitalization all increase with decreasing renal function (19). If measured with less error, cystatin C may be a more precise and accurate marker of impaired kidney function.

There are methodologic and statistical issues that need to be considered. It should be pointed out that in the study by Koenig et al. (12) the association was statistically significant only for those in the highest quintile of cystatin C. Although the test for trend was significant, this was driven by the association in the highest quintile. It would have been informative if, in addition to controlling for CRP and renal function, the authors had performed stratified analyses to evaluate whether the impact of cystatin C varied by CRP concentration and renal function. However, there were only 71 events, limiting their ability to perform subgroup analyses. Only a single measurement of cystatin C was reported; it is unclear whether a single measurement is sufficient to provide optimal predictive value. Unfortunately, there is insufficient information to determine a “safe” concentration of cystatin C. Furthermore, there is no information on the sensitivity and specificity of cystatin C as a predictor of the chosen endpoint. These test characteristics are necessary to evaluate the clinical utility of this biomarker. Finally, other studies are needed to evaluate how informative this biomarker will be in individuals without preexisting cardiovascular disease.

Although the study by Koenig et al. (12) focused on individuals with normal or mildly reduced renal function, the role of biomarkers has also been studied in patients with end-stage renal disease, typically those being treated with hemodialysis. The predictive ability of other biomarkers for cardiovascular outcomes was reported recently (20) and reviewed in Clinical Chemistry (21).

Other unresolved issues remain. Is cystatin C directly pathogenic as has been proposed for CRP? If not, for what process is it a marker? What additional factors, beyond age, race, sex, weight, and smoking, influence cystatin C concentrations? What interventions and/or medications lower cystatin C? Will interventions to decrease cystatin C reduce adverse events? How does this marker compare with others that have been found to predict adverse outcomes in hemodialysis patients, such as cardiac troponin T and I? In addition, would the results have changed with use of a different renal-function-estimating equation, such as the MDRD formula?

The results of the study by Koenig et al. (12) require confirmation in larger studies in which other purported biomarkers are simultaneously analyzed to begin to quantify the independent and additive effects of individual biomarkers. It is likely that no single biomarker will be perfectly predictive, but identifying the optimum combinations to develop risk stratification scores may allow targeted intervention trials to determine whether therapies designed to impact these biomarkers or their relevant pathways do in fact reduce morbidity or mortality. This is critical to reduce the frequency of the primary cause of death in this patient population.

References

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