Acute kidney injury (AKI) may be the real epidemic kidney disease, and practicing nephrologists have long known that patients with reduced GFR are more likely to experience AKI, particularly in the elderly. Surprisingly, this relationship had not been quantified rigorously until recently. For example, the widely disseminated Clinical Practice Guidelines for Chronic Kidney Disease by the National Kidney Foundation devote specific chapters describing the association of levels of GFR with various sequelae of chronic kidney disease (CKD) such as anemia, but there is no discussion of the association of level of GFR with AKI.

A publication in 2008 quantified the risk for dialysis-requiring AKI among a large cohort of patients who were receiving usual medical care in a Northern California integrated health care delivery system. The observed magnitude of the increase in odds ratio of AKI with progressively more severe CKD—up to 20- to 30-fold higher adjusted risk—suggests that AKI may be the sequel of CKD most tightly linked with estimated GFR (eGFR). This study also noted that proteinuria, a valuable screening marker for CKD, was also an important independent risk factor for AKI. Patients with documented dipstick proteinuria seem to be two to three times as likely to develop AKI, independent of eGFR. Notably, the relationship between proteinuria and risk for AKI had not been investigated in previous studies.

The study by Grams et al. in this issue of JASN is a timely and important addition to the literature. For the first time, the graded relationship was quantified between severity of proteinuria (albuminuria) and risk for AKI. Using participants with urine albumin-creatinine ratios <10 mg/g as a reference, the adjusted relative hazards of AKI were 1.9, 2.2, and 4.8 for urine albumin-creatinine ratio groups of 11 to 29, 30 to 299, and ≥300 mg/g, respectively.

The authors also quantified the graded relationship between eGFR and risk for AKI and the observed relative risks were similar to what had been reported. For example, the adjusted risk for AKI approximately doubles going from eGFR of 60 to 45 ml/min per 1.73 m². There is no interaction between the effects of low eGFR and high albuminuria.

The strengths of this study include the unbiased, precise assessment of albuminuria as part of a research protocol; the representative study population; and the thoroughness of the sensitivity analyses. For example, because eGFR may decline over time—especially among those with more albuminuria—it was useful and reassuring to repeat the analysis limited only to those who developed AKI relatively close to the time of quantifying albuminuria. Because albuminuria is a strong risk factor for cardiovascular disease, it is possible those with albuminuria are more likely to undergo cardiac catheterization or cardiac bypass surgery, which directly leads to AKI, so it was appropriate to repeat the analysis excluding these patients.

Limitations of the study by Grams et al. should also be mentioned. Only acute renal failure diagnostic codes were used to ascertain AKI, specifically International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes 584.5 to 584.9 (or ICD-10-CM codes N17.0 to 17.9; dialysis was identified using ICD-9 and ICD-10 codes 39.95, 38.95, V39.95, V45.1, V56.0, V56.1, Z49.0, Z49.1, and Z99.2). Previous epidemiologic studies have also used 584.5 to 584.9 or 584.x2 (which are the same), but these codes are known to be insensitive compared with the current gold standard definition of AKI on the basis of observed acute changes in level of serum creatinine; however, the observed associations would seem unlikely to be due to this bias. In contrast, the reported incidence of AKI is almost certainly unreliable. In this aspect, it is reassuring that the observed relative risks from this study regarding eGFR and risk for AKI are similar to that from a previous rigorous study that did not rely on diagnostic codes to identify cases of AKI and verified case ascertainment by direct audit of a random subset of charts. Another limitation of this study is that few enrollees had advanced CKD; hence, the confidence intervals for the hazard ratio estimates at low GFR levels are very wide.

A full appreciation of the significance of the study by Grams et al. merits discussion of the larger context. There has been considerable debate recently about the definition of CKD. Doubts have been raised as to whether a GFR cutoff of 60 ml/min per 1.73 m² is appropriate to define CKD. To inform this debate, one major thrust of active research in the field of CKD is to define better the association between levels...
of eGFR and various clinical outcomes. It is interesting that Grams et al. found that even those with an eGFR of 60 ml/min per 1.73 m² had adjusted relative hazards for AKI nearly twice as high as those with eGFR 75 ml/min per 1.73 m². This is a stronger and earlier signal than that seen in studies of eGFR and death or cardiovascular disease—where in numerous instances of risk may not rise appreciably until eGFR is <45 ml/min per 1.73 m². The finding that albuminuria has a strong linear relation with risk for AKI without apparent threshold is consistent with other recent studies that emphasized the critical importance of proteinuria in risk-stratifying patients with CKD.

Examining AKI as an outcome is hence a crucial but understudied area that will inform the classification of CKD. The pathophysiology of AKI is more directly linked to CKD than other adverse outcomes, such as cardiovascular disease or death, so any observed association between CKD and AKI is less likely to be due to confounding than analogous associations between CKD and cardiovascular disease or death.

Now that the shapes of the association between lower GFR, higher proteinuria, and risks for AKI have been outlined, future research should focus on how this information translates into improved patient outcomes. For example, what is the mechanism linking albuminuria to increased risk for AKI? Would interventions that lower albuminuria reduce the risk for AKI? These and other important questions urgently need understanding.

ACKNOWLEDGMENTS

This work was supported by grants DK77720, DK82223, and DK85649 from the National Institute of Diabetes and Digestive and Kidney Diseases/National Institutes of Health.

DISCLOSURES

None.

REFERENCES


See related article, “Albuminuria and Estimated Glomerular Filtration Rate Independently Associate with Acute Kidney Injury,” on pages 1757–1764.