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Risk Factors for ESRD: Lessons From a Community Study and Implications for Public Health

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Kidney failure is becoming more common in the United States, likely reflecting an aging population with increasing rates of diabetes, hypertension, and obesity. Despite the rising prevalence of kidney failure and the increasing socioeconomic and public health importance of kidney disease,¹ few longitudinal community studies have examined the association between risk factors for kidney disease and the development of kidney failure. This reflects the many challenges inherent in these studies, including: (1) kidney failure, which is often associated with cardiovascular disease (CVD), is a far less common outcome of kidney disease than death because of other conditions associated with CVD (the concept of competing risk); (2) cohorts derived from administrative data, although reasonably well suited to evaluate less common outcomes, may have inaccurate or biased risk factor ascertainment; (3) ascertainment of accurate kidney function, particularly when administrative data has been used, remains difficult because of limitations associated with serum creatinine measurement, glomerular filtration rate (GFR) estimation and chronic kidney disease (CKD) determination²; and (4) not all individuals with kidney failure receive kidney replacement therapies. In this issue of the *American Journal of Kidney Diseases*, a study by Bash and colleagues on risk factors for kidney failure overcomes many of these limitations to present a detailed report of risk factors for end-stage renal disease (ESRD).³

Kidney failure treated by dialysis and transplant is administratively defined as ESRD in the United States. Because Medicare funds the majority of ESRD care, epidemiologic data describing individuals with ESRD in the United States are widely available through the US Renal Data System (USRDS). These data frame the upcoming challenge that will be faced by both the US healthcare system as well as other nations with similar demographic and population trends. Specifically, in the United States, there has been continued growth in the prevalence of ESRD, to 1,665 per million in 2007 (approximately 530,000 individuals) despite relatively stable incidence of 354 per million population.⁴ Certain characteristics of the ESRD population demonstrate troubling trends that suggest potential targets for future research and intervention, including ESRD incidence and prevalence rates in African Americans approximately 4 times higher than rates in whites, as well as a continued rise in diabetes and hypertension as the listed causes for ESRD (54% and 33%, respectively). Ominously, the prevalence of ESRD is projected to increase to 775,000 by 2020.⁴

While progress has been made at slowing the growth in the incidence rate of ESRD in the United States, further advances will be essential, particularly given the tremendous financial

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and societal costs associated with kidney replacement therapies.⁵ Critical to continued progress is identification of those individuals in the general population at greatest risk of developing kidney failure. Currently, there are multiple identified risk factors for kidney failure, although most have been identified using USRDS data or using studies of populations with CKD. The National Kidney Foundation's 2002 Kidney Disease Outcomes Quality Initiative (KDOQI) guideline for evaluation, classification, and stratification of CKD describes initiation and progression factors for CKD including diabetes, hypertension, autoimmune diseases, infections, family history, low birth weight, and obstruction.⁶ Notably missing from this list were other risk factors for CVD and CVD itself. Later, several population-based studies identified CVD and obesity as risk factors for both subsequent CKD and ESRD.⁷⁻¹¹

The study by Bash et al builds on the findings of the most significant community-based study to date, Hsu and colleagues' examination of data from the Kaiser Permanente of Northern California managed care organization for identification of ESRD risk factors.¹² In that study, Hsu and colleagues analyzed a cohort of 177,570 patients who volunteered for health checkups between 1964 and 1973, of whom 842 (0.5%) developed ESRD. Risk factors associated with subsequent ESRD included higher levels of proteinuria as assessed by dipstick, obesity, higher serum creatinine and uric acid levels, nonwhite race (particularly being African American), lower education status, hypertension, and diabetes. There was an interesting relationship between age and ESRD, as individuals aged 60 years and older at the time of baseline assessment were at lower risk of developing ESRD; this likely reflects the availability of and societal mores towards offering dialysis for older individuals in the 1970s and 1980s, but may also reflect the competing risk of mortality among older individuals. Limitations of this important study include the reliance on administrative data for identifying risk factors and the presence of only individuals with insurance in the population.

In their study, Bash and colleagues report on the incidence of ESRD in the Atherosclerosis Risk in Communities (ARIC) Study, one of the most successful cardiovascular cohort studies in the United States. The ARIC Study cohort is a community-based population of noninstitutionalized adults aged 45-64 years from 4 US communities, with no preselection for kidney disease.³ Major strengths of the ARIC cohort include thorough ascertainment of CVD risk factors and outcomes, indirect calibration of baseline creatinine levels, longitudinal follow-up through the 1990s and 2000s when dialysis became more widely available, and a study design geared to achieving racial and socioeconomic diversity. The most substantial limitation is the absence of baseline data on proteinuria. Additionally, event surveillance in ARIC was geared to CVD and not kidney disease ascertainment; accordingly the authors developed schema to assess ESRD through a combination of hospital surveillance, International Classification of Diseases codes, and death certificate data. Accordingly, while some patients with acute progression of CKD who did not elect to receive kidney replacement therapy may be classified as developing ESRD, others with chronic kidney failure may not have been captured.

Over 17 years, 241 (1.6%) ARIC participants developed ESRD; risk factors included older age, estimated GFR (eGFR) values below 90 mL/min/1.73 m² (1.5 mL/s/1.73 m²), African American race, diabetes, hypertension, coronary heart disease history, higher body mass index, higher serum triglycerides, male sex, and current or former smoking status. Interestingly, a slightly increased risk was also associated with eGFR levels above 120 mL/min/1.73 m² (2 mL/s/1.73 m²). Using population-attributable risks, diabetes and hypertension, not surprisingly, accounted for over one-half of incident ESRD cases.

Several of these findings warrant further discussion. First, triglyceride level was a robust predictor of elevated ESRD risk despite no significant increased risk associated with other lipid measures. The cause of this relationship is uncertain and not previously described in a

population study; accordingly, it is possible that triglyceride level may be a proxy for proteinuria rather than a modifiable cause of progression. A second notable finding is the relationship between body mass index and subsequent ESRD. Although not a powerful predictor, body mass index remained borderline significant despite it not being an optimal measure of obesity in CKD,¹³ likely having a J-shaped relationship with ESRD risk, and being included in models that already adjusted for the likely mediators of kidney disease in obesity, namely hypertension and diabetes.¹⁴ Third, the curvilinear association between eGFR and ESRD is compelling, and the presence of increased ESRD risk among those with the highest eGFR values is a novel finding. Although J-shaped relationships between creatinine-based GFR estimates and mortality have previously been demonstrated,¹⁵ the prevailing opinion has been that low serum creatinine levels in the population identify individuals with low muscle mass and, accordingly, higher risk of mortality. In this study of relatively young and middle-aged individuals, lower serum creatinine levels may indicate diseases that cause glomerular hyperfiltration (most of the patients in the current study with lower baseline eGFR and subsequent progression to ESRD had type 2 diabetes).¹⁶ Finally, the continued presence of increased risk of ESRD among African Americans, whereby there was 4 times the incidence of ESRD among African Americans in ARIC as compared with whites and a markedly increased risk of ESRD despite adjustment for many comorbid conditions, illuminates a critical public health imperative in the United States and is one that requires continued research to better understand and prevent.

In summary, Bash and colleagues have illustrated the major risk factors for ESRD in a current community population. Taken in conjunction with analyses by Hsu and colleagues and data from the USRDS, the study by Bash and colleagues offers a reasonably thorough picture of ESRD risk factors in the general population. Each of these cohorts complement weaknesses inherent in the others, and, when viewed collectively, reveal ESRD as a major public health issue that will have enhanced significance in the years to come. In light of the aging population, the continued rise in obesity-associated diseases (specifically hypertension and diabetes), and the high population-attributable risk of ESRD demonstrated by Bash and colleagues that is associated with these conditions, it is safe to state that prevention of kidney failure will continue to assume increasing importance in the years to come. These studies help demonstrate our continuing challenge and illustrate potential targets where, on a population scale, a real effect could be made.

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