The disproportionate burden of kidney failure in Black Americans is well recognized, but this racial and ethnic kidney health disparity does not emerge until late-stage CKD. In communities of color, social determinants interact with human biology in multilevel, complex ways that are poorly understood but clearly lead to health inequities in chronic conditions, such as kidney disease.

The coronavirus disease 2019 (COVID-19) pandemic provides sobering evidence of the impact of social determinants of health. COVID-19–related infection, hospitalization, and death have disproportionately affected Black communities, and overall US mortality has been linked to social determinants of health (1). COVID-19–related kidney injury occurs in up to one third of hospitalized patients. However, significant variation has been observed worldwide. In a national cohort of hospitalized US veterans, 31% of the COVID-19–related AKI geographic variation could be explained by the percentage of Black individuals with COVID-19 infections in the hospital systems studied (2). In addition to the devastating outcomes we are currently witnessing, future consequences of this pandemic may be an increased prevalence of kidney disease and a widening gap of kidney health disparities. As then US Senator, now Vice President, Kamala D. Harris said, “The COVID-19 pandemic has shone a bright light on… racial and gender disparities within our economic system that have persisted for far too long.”

In addition to social factors, is there a biologic susceptibility in Black individuals contributing to the manifestation of AKI? In this issue of CJASN, Larsen and coauthors suggest that the burden of COVID-19–related kidney injury may be associated with APOL1 kidney risk variants (3). These polymorphisms are common in people of West African ancestry and robustly associate under a recessive model of inheritance with nondiabetic CKD (4) but have not previously been shown to associate with AKI. Most individuals who carry kidney risk variants never develop clinically significant CKD, suggesting that a second stress is necessary for onset and/or progression of kidney injury. This study reports, for the first time, that Black Americans with homozygous APOL1 risk alleles who were hospitalized in New Orleans with COVID-19 infection were four-fold more likely to develop AKI, three-fold more likely to have prolonged AKI, and five-fold more likely to have severe AKI requiring kidney replacement therapy than those with 0 or 1 risk alleles. Prior to the COVID pandemic, two genome wide association studies using much larger cohorts have failed to demonstrate an association of APOL1 with AKI, although one of these studies identified AKI-associated variants near a regulator of APOL1.

Mechanisms of APOL1’s trypanosome-killing activity have been the prime drivers of hypotheses about APOL1–associated chronic kidney injury pathways but, at least in terms of tempo, may better model AKI (5). Most of these studies have proposed gain-of-function, variant-dependent cytotoxicity, which occurs with cytokine-driven APOL1 expression, as the causal mechanism. Kidney risk variant APOL1s, but not reference APOL1, traffic to the plasma membrane and assemble into an acid-gated ion channel, which opens when exposed to normal pH and permits osmotic cell death. Other studies have demonstrated additional gain-of-function injury mechanisms for the risk APOL1s, including impaired cellular cholesterol efflux and lipid accumulation in tissue macrophages, mitochondrial or lysosomal dysfunction, and actomyosin reorganization from PI(4)-kinase IIIB (PI4KB) inhibition (5). Unstressed mice with APOL1 transgenes that permit constitutive expression do not develop kidney disease even after prolonged observation. Consistent with the need for a second hit, mice with G1, but not G0, fosmids did develop proteinuria when “stressed” with interferon-γ (6). More recently, interferon-treated mice with bacterial arterial chromosomes for kidney risk variants but not reference APOL1 developed proteinuria and glomerulosclerosis that mirrors some human APOL1–associated kidney diseases. Both of these animal models support a gain-of-function mechanism, although the molecular pathways mediating kidney injury remain unclear (7).

The observations by Larsen and colleagues are provocative, but the study sample is small and retrospective, subject to the unrecognized confounding biases due to its design. The authors suggest that APOL1 kidney risk variants may cause AKI from cell autonomous tubular toxicity, but despite early evidence that
APOL1 is expressed in proximal tubules, recent data suggest proximal tubules in situ either do not express APOL1 or express it at very low levels, even after interferon treatment (7,8). Of course, these earlier data do not address a possible interaction between COVID-19 infection and APOL1 causing AKI. Kidney proximal tubules highly express the receptor for the etiologic virus (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]), angiotensin-converting enzyme 2, but evidence of direct infection of kidney by SARS-CoV-2 remains at equipoise with supporting data almost exclusively shown in kidneys obtained at autopsy (9). In vitro work does suggest SARS-CoV-2 can infect kidney tubular cells, which after infection express interferon-regulated mediators although APOL1 was not assayed. Viral infection was not cytopathic but did appear to activate fibrosing pathways (10), perhaps providing an explanation for the greater rate of eGFR decline after hospital-associated AKI in COVID-19–infected patients (11).

Given the potential significance of an association of APOL1 kidney risk variants with AKI, the findings by Larsen et al. should be replicated with a larger, preferably national, diverse study population whose phenotypes include an assessment of COVID-19 illness severity and analyses with ancestry informative markers to assess for a false-positive association from confounding genetic population structure. Nonetheless, the results highlight the need for research to understand the full spectrum of biologic to mechanistic processes of kidney disease susceptibility.

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