Findings

In Women with ADPKD, Aneurysm Risk Increases after Age 50

An analysis of a large cohort of patients with autosomal-dominant polycystic kidney disease (ADPKD) adds new knowledge about risk factors for intracranial aneurysm (IA), including an increase in IA risk for women after menopause, according to a pre-proof paper in *Nephrology Dialysis Transplantation*.

The cross-sectional, population-based study included 2449 patients with ADPKD (median age, 55 years) from 26 nephrology centers in western France. On genetic analysis in 2386 patients, 67.6% had *PKD1* pathogenic variants, and 19.0% had *PKD2* pathogenic variants. The researchers analyzed the frequency of diagnosis of ruptured and unruptured IA, along with risk factors for this vascular complication.

At the time of enrollment, 4.65% of patients had previously been diagnosed with IA, ruptured or unruptured. Nearly one-half of patients had a positive family history of IAs. Aneurysms occurred at all stages of chronic kidney disease; most were small, saccular, and located in the anterior circulation. More than one-fourth of patients (26.3%) had multiple IAs.

Cumulative probability of IA diagnosis increased from 1.3% at age 40 to 3.9% at age 50, to 6.2% at age 60, and to 8.1% at age 70. Probabilities of ruptured aneurysm were 0.9%, 1.8%, 2.6%, and 3.2%, respectively.

In patients younger than 50 years old, IA risk was similar for men and women. After 50, however, IA risk was substantially higher in women: up to 10.8% compared with 5.4% in men. The frequency of IA diagnosis was more than twice as high in patients with *PKD2* pathogenic variants compared with *PKD1* variants. In addition to female sex and *PKD1* genotype, hypertension before age 35 and smoking were independent risk factors for diagnosed IA.

Patients with ADPKD are at high risk of IA. Risk factors for IA have important implications for screening using magnetic resonance imaging. In previous reports, a personal or family history has been the main risk factor for IA.

The new finding demonstrates the "complex and multifactorial" determinants of IAs in a large population of patients with ADPKD receiving real-life clinical care. Women appear more likely to be diagnosed with ruptured or unruptured IAs, particularly after age 50. The investigators note, "This parallels observations made in the non-ADPKD population and suggests a possible protective role of estrogens" [Lefèvre S, et al. Diagnosis and risk factors for intracranial aneurysms in autosomal polycystic kidney disease: A cross-sectional study from the Genkyst cohort. *Nephrol Dial Transpl*, published online ahead of print February 2, 2022. doi: 10.1093/ndt/gfac027; https://academic.oup.com/ndt/advance-article/doi/10.1093/ndt/gfac027/6520449?login=false]. ■

The Missing Link between Chronic Kidney Disease and Peripheral Arterial Disease

By Chelsea C. Estrada and Sandeep K. Mallipattu

Peripheral arterial disease (PAD) is three times as prevalent in patients with chronic kidney disease (CKD) compared with their non-CKD counterparts (1). This increased susceptibility has been attributed to the uremic milieu; however, specific mechanisms remain unknown. Recently, in the *Journal of Clinical Investigation*, Arinze and colleagues (2) shed new light on the detrimental impact of dietary and gut-converted, tryptophan-based uremic toxins (indoxyl sulfate and its metabolites) on neovascularization in PAD.

In a series of elegant studies, the investigators demonstrated that serum from patients with uremia, as well as indoxyl sulfate alone, induced a dose-dependent reduction in Wnt-β-catenin signaling in endothelial cells, which was exacerbated under hypoxic conditions. Interestingly, this effect was observed at levels of indoxyl sulfate consistent with that in patients with early-stage CKD. With the use of zebrafish and mouse models, the researchers demonstrated that this loss in Wnt-β-catenin signaling translated to decreased angiogenesis, capillary density, and vascular perfusion. The authors also identified that the reduction in active β-catenin was dependent on aryl hydrocarbon receptor activation. Importantly, in a mouse model of CKD and PAD, aryl hydrocarbon receptor inhibition restored Wnt-β-catenin signaling to that of non-uremic levels and restored neovascularization. The authors corroborated these findings in plasma from patients with CKD and PAD, where levels of indoxyl sulfate and its metabolites were predictive of subsequent adverse limb events in patients followed for up to 2 years.

Significant questions raised by these studies include the possibility of inhibiting aryl hydrocarbon receptor signaling as a therapeutic target in PAD, with or without CKD. Many of the same authors also previously demonstrated that aryl hydrocarbon receptor inhibition decreased the time to occlusion in a pro-thrombotic CKD murine model (3). Aryl hydrocarbon receptor inhibitors are currently in clinical trials for solid tumors and have been shown to reduce tumor growth when used in combination with immune checkpoint inhibition (4).

With the exceedingly high incidence of cardiovascular mortality in patients with CKD and kidney failure on dialysis, the role of aryl hydrocarbon receptor pathway antagonism in coronary circulation ischemia might also serve as another important avenue for future investigation. This study also resurfaces important questions that have been raised by nephrologists for decades: How can we optimize the dialysis prescription to enhance removal of these protein-bound tryptophan derivatives? Does modulating the dietary regimen to reduce the accumulation of indoxyl sulfate levels improve clinical outcomes? Taken together, Arinze et al. (2) highlight the critical need for randomized clinical trials to assess the therapeutic impact of targeting this pathway in patients with CKD and kidney failure on dialysis. ■

Chelsea C. Estrada, DO, and Sandeep K. Mallipattu, MD, FASN, are with the Division of Nephrology, Department of Medicine, Stony Brook University, Stony Brook, and Renal Section, Northport VA Medical Center, Northport, NY.

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