The Renal Tubulointerstitium

The renal tubulointerstitium is an often underappreciated compartment of the kidney but of great importance in acute kidney disease and CKD. As early as the 1970s, Bohle and colleagues[1] recognized that kidney function did not correlate well with the severity of glomerular disease but rather with the relative interstitial volume. We now know that the microenvironment encompassing the tubulointerstitium is composed of tubular epithelial cells, interstitial cells, peritubular capillary endothelium, pericytes, and extracellular matrix, which have complex structural and functional relationships. Profibrotic and inflammatory factors influencing this compartment are a major determinant of kidney disease progression. There is a crucial role of direct toxic, ischemic, and inflammatory injury to the renal tubules and interstitium in acute, progressive, and chronic kidney failure. Additionally, while glomerular damage, including glomerulosclerosis, associates with proteinuria and an active urinary sediment, the downstream effects on the tubulointerstitium are thought to result in the reduction of glomerular filtration rate.[2] When acute changes to the tubulointerstitium are not reversible, fibrosis ensues with chronic kidney failure progressing toward ESRD.

This issue of *Advances in Chronic Kidney Disease* is focused on acute and chronic tubulointerstitial kidney diseases as a reflection of the need to address maintaining kidney function in patients with any form of kidney injury. This is an increasingly important area in light of the apparent increasing incidence of acute interstitial nephritis particularly among the elderly, the prevalence of CKD which is estimated to affect 7%-10% of adults in the United States, and the relative rise in cases of more severe kidney impairment particularly in those aged 45-64 years despite a leveling off in the incidence of CKD overall.[3-5] The issue begins with an overview by Perazella of the clinical presentation and evaluation of the patient with tubulointerstitial disease. The use and limitations of laboratory studies, imaging, and kidney biopsy in the challenging diagnosis of interstitial nephritis are discussed. This is followed by articles on medications inducing interstitial nephritis. Medications have been used to treat illnesses for many millennia. Herbal and mineral medications were detailed in the Ebers Papyrus, a medical document discovered in Thebes dating from 1550 BC, which likely contains known information about previous medication usage copied from earlier texts. There has been an explosion of therapeutics since the late 19th century, with the discovery of medicines that can relieve pain, provide anesthesia, fight infections, and lessen or cure disease. The discovery of penicillin by Fleming in 1928, and the wide use of antibiotics during the latter part of World War II, ushered in an era of widespread drug use for everyday ailments and common diseases. However, medications are not without their complications. In 1899, Louis Lewin published Die Nebenwirkungen der Arzneimittel, a treatise on the unwanted effects of drug treatments. Subsequently, Leopold Meyler published a book in 1951 describing drug-related adverse events after he experienced deafness from dihydrostreptomycin and/or fever from para-aminosalicylic acid. In this issue, established and newer medications associated with interstitial nephritis are reviewed by Nast, and Raghavan details the mechanisms of delayed hypersensitivity response for this form of injury. Complimenting this, the fourth article by Nanavati and Herlitz reviews tubulointerstitial nephrotoxic effects and secondary mechanisms of injury, such as ischemia due to drugs of abuse. This is a constantly changing landscape because of the ever-expanding number of available recreational substances.

The following 3 articles address specific variants of tubulointerstitial disease. Bleyer and colleagues review the clinical features and genetics of autosomal dominant tubulointerstitial kidney disease. This rare entity can affect a substantial number of members in a family and affords opportunities to study interactions among genes and the environment and identify therapeutic approaches to this progressive set of diseases. IgG4-related disease is discussed by Zhang and Cornell. This autoimmune fibroinflammatory lesion is part of a systemic disease process of unknown pathogenesis. The authors point out the importance of obtaining historical or current evidence of other organ involvement, although the kidney may be the only organ affected. Awareness of this lesion and including it in a differential diagnosis in the appropriate setting is important, as typically there is a good response to steroid therapy although relapses are not uncommon. Orantes-Navarro and colleagues describe the features of, and examine possible pathogenetic mechanisms for, the poorly understood chronic interstitial nephritis in agricultural communities. This entity, which also has been termed Mesoamerican nephropathy and CKD of unknown cause, is a major public health crisis in several countries in Central America and Asia. In El Salvador, this chronic tubulointerstitial nephropathy has resulted in a 50% increase in hospitalizations for CKD from 2005 to 2012 and is the leading cause of hospital deaths. Chronic interstitial nephritis in agricultural communities results in a 4-fold increase in deaths because of CKD compared with worldwide rates, particularly in men aged 20-49 years living and working in agricultural communities. Considerable work is being done to determine the etiologies of this malady, which are likely multifactorial, and to develop preventive measures to abrogate this devastating form of progressive kidney disease.

The final 2 articles in this issue address kidney fibrosis. Schnaper reviews mechanisms of progressive kidney fibrosis, which are believed to originate within the tubular epithelium. This article highlights the role of injured tubular cells in induction of inflammatory and fibrogenic responses, with misdirected repair, maladaptive

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responses, and progressive nephron loss. These processes are thought to be a final common pathway in all kidney disease progressing to CKD. Lastly, Boor and colleagues discuss the current state and future direction of treatments aimed at preventing the development and worsening of kidney fibrosis. They point out the lack of specific therapies directed at the kidneys and the challenges in identifying effective treatments with acceptable side effect profiles. The need for improved companion diagnostics, patient selection, biomarkers, and targeted interventions is highlighted.

With the burgeoning elderly population, upsurge in acute and chronic tubulointerstitial lesions and role of the tubulointerstitium in the progression of all forms of kidney disease, the tubules and interstitium come into focus as an important frontier in the battle against CKD and AKI. This issue of *Advances in Chronic Kidney Disease* provides a timely look at this renal compartment including recognizing the various forms of tubulointerstitial injury and making timely diagnoses. New ways of measuring and interrogating tubulointerstitial injury and fibrosis are under investigation, with the goal of understanding the responsible pathogenetic mechanisms. This may allow for development of targeted therapies to reverse acute injury, prevent disease progression, and reach the holy grail of reversing established tubulointerstitial fibrosis.

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REFERENCES

1. Bohle A, Grund KE, Mackensen S, Tolon M. Correlations between renal interstitium and level of serum creatinine. Morphometric investigations of biopsies in perimembranous glomerulonephritis. *Virchows Arch A Pathol Anat Histol.* 1977;373(1):15-22.
2. Zeisberg M, Strutz F, Müller GA. Renal fibrosis: an update. *Curr Opin Nephrol Hypertens.* 2001;10(3):315-320.
3. Praga M, Sevillano A, Auñón P, González E. Changes in the aetiology, clinical presentation and management of acute interstitial nephritis, an increasingly common cause of acute kidney injury. *Nephrol Dial Transplant.* 2015;30(9):1472-1479.
4. US Renal Data System USRDS. *2009 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States.* Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2009.
5. Hsu CY, Vittinghoff E, Lin F, Shlipak MG. The incidence of end-stage renal disease is increasing faster than the prevalence of chronic renal insufficiency. *Ann Intern Med.* 2004;141(2):95-101.