GUEST EDITORIAL

Glomerular Grievances and CKD

Glomerular disease has been estimated to occur in approximately 18 per 100,000 people, although the exact incidence is difficult to determine.[1] Factors such as recognition of urinary abnormalities, renal biopsy practice, infections, health resources, socioeconomic conditions, and environmental factors significantly affect the incidence of glomerular disorders, which actually may be higher than reported. In addition, systemic and vascular diseases such as diabetes and hypertension substantially increase the incidence of nephropathies associated with CKD. In the United States in 2008, the primary cause of ESRD was glomerulonephritis in 15% of cases, diabetes in 38%, and hypertension in 24%.[2] Additionally, it has been estimated that there is as much as a 50-fold increase in the number of patients with earlier stage CKD who have not yet reached end-stage renal failure.[3] Patients with systemic diseases often do not undergo renal biopsy, and are provided with a diagnosis empirically. However, if a kidney biopsy is subsequently performed, additional glomerular or tubulointerstitial disorders may frequently be diagnosed. Therefore, glomerulopathies play a significant role in the increasing global incidence of CKD and renal failure.

Key questions surrounding glomerular disorders include why different glomerulopathies progress to renal failure at varying rates, and why patients with the same disease also have variability in the time of progression to CKD. This suggests that the response is more complex than a general fibrotic or scarring reaction, and that underlying risk factors such as genetic predisposition, racial predilection, low birth weight, older age, and comorbidities including diabetes, hypertension, obesity, smoking, infection, and other environmental or epigenentic factors modulate the fate of the glomerulus and tubulointerstitial compartment. The ultimate result may be the development of glomerulosclerosis, interstitial fibrosis, and tubular atrophy, with chronic renal functional impairment. Additionally, intracellular and intercellular signaling within the glomerular microenvironment, such as communication among the resident glomerular cells, likely is an important factor in influencing progression of glomerular disease to segmental or global sclerosis. The mechanisms involved in dysregulation and malfunction of glomerular cells are complex, and have recently been studied extensively in the podocyte. The critical role of the podocyte in this regard is also reflected by the fact that glomerular proteinuria is a known independent risk factor for progression of renal disease, and is linked to direct and indirect damage to the tubulointerstitium.

This issue of *Advances in Chronic Kidney Disease* focuses on the relationship between glomerular injury and CKD. The role of damaged glomeruli in initiating or exacerbating renal parenchymal scarring is addressed by discussing different forms of glomerulonephritis and glomerulopathies. Attention is given to aging, starting with the article by Bomback and colleagues, which discusses the incidence of glomerular lesions in the elderly. Although age- and systemic comorbidity-related renal diseases are common in this cohort, there also are glomerulopathies and other renal diseases in the elderly and very elderly population that may be amenable to treatment, providing a rationale for renal biopsy in this patient population. The epidemiology and changing demographics and morphology of postinfectious glomerulonephritis are reviewed in the article by Nast, showing that the prevalence of this lesion in older patients with comorbidities is associated with a worse outcome and a higher incidence of resulting CKD. The pathogenesis of age-related glomerular injury is further addressed in the article by Barisoni, which reviews mechanisms of podocyte injury and glomerular sclerosis associated with the aging processes. This thorough review also highlights the relationships of podocyte injury to glomerular disease onset, progression, and repair.

Complement plays a critical part in the pathogenesis of glomerular lesions, and this is examined in the review by Vernon and Cook. It is important to understand how complement functions in a primary or secondary role in a variety of renal and glomerular diseases to mediate renal tissue damage and enhance scarring. Building on this, the article by Satirapoj and colleagues proposes mechanisms by which glomerular injury and proteinuria may induce tubulointerstitial inflammation and fibrosis. This tubular damage may also provide the source of urinary biomarkers, which can be used to assess progression of chronic renal injury and functional impairment.

Morphologic features of renal biopsies may provide information regarding disease pathogenesis and prognosis independent of clinical or other laboratory data. Abnormal forms of collagen accumulate in glomeruli in infrequent lesions such as type III collagen glomerulopathy and nail patella syndrome, described in the article by Cohen. These fibrosing lesions, often an expression of a genetic disease, demonstrate how glomerular accretion of extracellular material may be the central feature of a progressive glomerulopathy, and not merely a response to injury. Histopathologic identification of acute and chronic renal parenchymal features can be used to develop clinically relevant scoring systems, as discussed

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for IgA nephropathy in the article by Haas and Reich. Specific morphologic criteria can indicate which patients are at risk for progression and which may respond to immunosuppressive treatment, allowing for more effective therapeutic intervention. Morphology may also be used to categorize and assess molecular data, further clarifying potential pathogenetic mechanisms. However, under certain circumstances, additional diagnostic tests are required, such as serologic identification of anti-phospholipase A2 receptor and other autoantibodies in membranous glomerulopathy, as discussed in the article by Segal and Choi. In addition to contributing to the understanding of disease pathogenesis, these autoantibodies may be useful markers for disease monitoring and to guide the use of new methods of treatment to prevent disease progression.

Although many questions about the role of the glomerulus and its resident cells in initiating and exacerbating renal fibrosis and CKD remain unanswered, some light has been shed on the mechanisms by which glomeruli become injured and sclerotic, how glomeruli induce chronic tubulointerstitial changes, and possible approaches to means of predicting and preventing CKD in the setting of glomerulopathies and glomerulonephritis.

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