MAYO CLINIC

Disease Progression and End-Stage Renal Disease in Diverse Glomerulopathies

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Chronic kidney disease (CKD) is not a functionally static process but rather a potentially progressive one that may culminate in end-stage renal disease (ESRD). The onset of ESRD is a turning point in the course of CKD because ESRD substantially alters the patient's lifestyle and imposes increased morbidity and mortality in patients so afflicted. For most patients, ESRD is managed by in-center hemodialysis, a treatment modality that obligates, among other requirements, the placement and functionality of a vascular access for hemodialysis; the need to travel thrice weekly to the dialysis center; thrice-weekly hemodialysis treatments lasting 3 or more hours; tolerance to the recurrent lassitude and generalized lack of well-being often experienced after each hemodialysis treatment; and restricted intake of fluids and assorted dietary constituents. Home dialysis programs are based either on hemodialysis or on peritoneal dialysis, and although obviating travel to a dialysis center, these programs place substantial responsibility on the part of the patient in delivering home-based dialytic care. A living-donor kidney transplant is the treatment of choice for ESRD, but many patients with ESRD may not have such options and are thus managed by dialysis for years while awaiting deceased-donor kidney transplantation. For either type of kidney transplantation, daily immunosuppressive therapy becomes a lifelong requirement.

Preserving renal function in patients with CKD and avoiding or delaying the onset of ESRD are thus fundamental objectives in the management of patients with CKD.[1] Decline in renal function in CKD results from progressive pathogenetic processes instigated in the diseased kidney upon which may be superimposed acute potentially reversible insults such as compromised renal perfusion, nephrotoxic medications/agents, and postrenal obstruction. Therapeutic strategies generally applied to retard the progression of CKD, irrespective of the underlying cause, include avoidance and/or correction of such intermittent insults; adequate blood pressure control, in particular, by angiotensin-converting enzyme inhibitor (ACEI)-based or angiotensin receptor blocker (ARB)-based regimens; reduction of proteinuria by ACEIs or ARBs; management of acidosis and hyperphosphatemia; moderate dietary protein restriction; and control of blood glucose in patients with diabetes mellitus. In addition to these generic therapeutic strategies, certain types of CKD are amenable to targeted, disease-specific therapies.

In this issue of the *Proceedings*, Sim et al[2] question whether the rate of progression of CKD and incident ESRD differ among patients with specific types of glomerulopathies. Chronic kidney disease can arise from disease processes that afflict initially and principally specific compartments of the kidney and these include vasculitides, glomerulopathies, and tubulointerstitial nephritides. As compared with tubulointerstitial nephritides, glomerulopathies, as a group, generally exhibit a more marked time-dependent decline in renal function and a greater risk for ESRD, both outcomes likely reflecting the higher amounts of proteinuria that occur in glomerulopathies. Glomerulopathies, however, are heterogeneous in nature, with glomerulopathies differing in any one of a number of ways that include the extent to which immune, inflammatory, or sclerosing processes are involved in the specific type of glomerulopathy; the tempo with which such processes occur; the types of cells in the glomerular compartment that principally participate in the glomerulopathy; and whether the glomerulopathy is the manifestation of a kidney-restricted disease or the consequence of a systemic disease or extrarenal process.[3]

Sim et al[2] undertook a retrospective cohort study using the electronic health records of the Kaiser Permanente Southern California integrated health system to analyze outcomes in patients who underwent a kidney biopsy between January 1, 2000, and December 31, 2011.[2] Rate of decline of renal function, incident ESRD, and death were

compared among 5 common glomerulopathies: focal segmental glomerulosclerosis (FSGS), membranous nephropathy (MN), minimal change disease (MCD), IgA nephropathy (IgAN), and lupus nephropathy (LN). The study population included 2350 patients with glomerulopathies who were followed for a mean duration of 4.5 years. The findings demonstrate that 21.1% of patients progressed to ESRD and 8.3% died before the onset of ESRD. The median decline in estimated glomerular filtration rate was 1.0 mL/min/1.73 m^2 per year, with FSGS exhibiting the highest rate of progression followed by MN and IgAN; the incident ESRD rates were also highest for FSGS, and sequentially less so for IgAN, LN, MN, and MCD.[2]

Sim et al[2] point out that a strength of their study is that it draws upon a large heterogeneous population wherein patient care is not tertiary center–based, but provided in the clinical community of medical centers and clinics of a single integrated health care system.[2] Glomerulopathies, along with diabetic and hypertensive nephropathies, are among the major contributors to ESRD, but are not common diseases. Patients with glomerulopathies are often referred to tertiary centers for evaluation and management, both of which may be undertaken as part of clinical trials involving multiple such centers. Patients with glomerulopathies refractory to therapy or with treatment-related side effects are often managed at tertiary centers. As noted by Sim et al,[2] much of the current literature regarding rates of progression and ESRD in glomerulopathies is based on such tertiary center experience and on relatively smaller and/or specific patient populations. The study by Sim et al[2] thus complements and advances the current literature because its sample size is large; the cohort is drawn from the large membership (>4.2 million) of an integrated health care system that serves a distinct geographic region (Southern California) and broadly provides consistent and comparable care for its membership; membership of this health care system is heterogeneous as regards race, ethnicity, and socioeconomic status; and the follow-up of patients is relatively long.[2]

Among the 5 glomerulopathies studied by Sim et al,[2] FSGS exhibited the largest renal functional decline, the highest ESRD incidence, and the lowest ESRD-free survival.[2] This propensity for brisker progression to ESRD has been observed in previous studies.[4] It should be noted that even within FSGS, as is true for other glomerulopathies, there are specific subtypes that behave and are treated differently.[5,6] FSGS is a histologic lesion that may reflect 1 of 3 main mechanisms: (1) primary FSGS that is caused by an immunologic/cytotoxic process that targets the podocyte and is commonly associated with the nephrotic syndrome and progressive loss of renal function; (2) secondary FSGS that is caused by assorted diseases (eg, obesity, drug-induced, and reflux nephropathy) in which proteinuria is often subnephrotic and renal functional decline slower than in primary FSGS; and (3) FSGS that is secondary to genetic defects.[5,6] It would be of interest to determine what percentage of patients with FSGS were represented by each of these subtypes, in particular, by primary FSGS, in view of the higher risk of this subtype to progress to ESRD; notably, proteinuria in patients with FSGS studied by Sim et al[2] ranged from subnephrotic levels to massive proteinuria. As regards the issue of heterogeneity within a specific glomerulopathy, this is perhaps best illustrated by LN, 1 of the 5 glomerulopathies studied by Sim et al[2]; there are 6 distinct classes of LN, 1 of which is MN, a glomerulopathy also numbering among the 5 analyzed in this study.[7]

Two salient imponderables in this study include the relative threshold for individual physicians to undertake a kidney biopsy in patients with CKD and their use of immunosuppressive medications in the treatment of glomerulopathies. Hypertensive patients with relatively low-grade proteinuria or hyperglycemic patients with whatever degree of proteinuria may be diagnosed as having hypertensive nephropathy or diabetic nephropathy, respectively, when, indeed, there is an underlying glomerulopathy, the latter missed in the absence of a kidney biopsy. Although there are guidelines and expert opinions regarding the use of steroids and immunosuppressive medications in the treatment of glomerulopathies, there is individual physician variability in the specific choice of such therapy, when to initiate it, and how long such therapy is maintained; all these variables may influence outcomes in a given glomerulopathy as regards disease progression and the onset of ESRD.

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The study of Sim et al[2] is important from several perspectives, in particular, in its highlighting of an underlying glomerulopathy as a determinant of the rate of loss of kidney function and in its evaluation of the relative rates of functional decline when patients with glomerulopathies are diagnosed and managed in the clinical community setting of an integrated health care system. Accurately diagnosing a specific glomerulopathy as the underlying cause for CKD may not only determine the need for specific immunotherapy but may also prognosticate on the course of such disease and the relative risk for ESRD. Finally, in the field of glomerular disease, there is considerable effort to develop more targeted therapies, the specificity and efficacy of which are expected to increase in the coming years.[8,9] The implementation of such therapies requires an understanding of the general course of disease in specific glomerulopathies, and, in this regard, Sim et al[2] are to be congratulated for their timely contribution to the current literature.

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REFERENCES

1. Webster AC, Nagler EV, Morton RL, Masson P. Chronic kidney disease. *Lancet*. 2017;389(10075):1238-1252.
2. Sim J, Bhandari S, Batech M, et al. End stage renal disease and mortality outcomes across different glomerulonephropathies within a large diverse US population. *Mayo Clin Proc*. 2018; 93(2):167-178.
3. Sethi S, Haas M, Markowitz GS, et al. Mayo Clinic/Renal Pathology Society Consensus Report on Pathologic Classification, Diagnosis, and Reporting of GN. *J Am Soc Nephrol*. 2016;27(5): 1278-1287.
4. Chou YH, Lien YC, Hu FC, et al. Clinical outcomes and predictors for ESRD and mortality in primary GN. *Clin J Am Soc Nephrol*. 2012;7(9):1401-1408.
5. Hommos MS, De Vriese AS, Alexander MP, et al. The incidence of primary vs secondary focal segmental glomerulosclerosis: a clinicopathologic study. *Mayo Clin Proc*. 2017;92(12):1772-1781.
6. De Vriese AS, Sethi S, Nath KA, Glassock R, Fervenza FC. Differentiating primary, genetic, and secondary FSGS in adults: a clinicopathologic approach. *J Am Soc Nephrol*. 2018.
7. Yu F, Haas M, Glassock R, Zhao MH. Redefining lupus nephritis: clinical implications of pathophysiologic subtypes. *Nat Rev Nephrol*. 2017;13(8):483-495.
8. Zand L, Glassock RJ, De Vriese AS, Sethi S, Fervenza FC. What are we missing in the clinical trials of focal segmental glomerulosclerosis? *Nephrol Dial Transplant*. 2017;32(Suppl 1):i14-i21.
9. Thurman JM. Many drugs for many targets: novel treatments for complement-mediated glomerular disease. *Nephrol Dial Transplant*. 2017;32(Suppl 1):i57-i64.