Editorial

Temporal Trends in the Epidemiology of Biopsy-Proven Glomerular Diseases: An Alarming Increase in Diabetic Glomerulosclerosis

Jean Hou and Mark Haas

Department of Pathology and Laboratory Medicine, Cedars-Sinai Medical Center, Los Angeles, California

Correspondence:
Dr. Mark Haas, Department of Pathology and Laboratory Medicine, Cedars-Sinai Medical Center, 116 North Robertson Boulevard, Suite 500, Los Angeles, CA 90048. Email: mark.haas@cshs.org

The epidemiology of ESRD has been extensively studied and is well characterized. For example, the US Renal Data System (USRDS) is a national data system that collects and analyzes critical information regarding CKD and ESRD in the United States as a whole, plus information for specific geographic regions. Although primary glomerular diseases represent the third most common cause of ESRD in adults and the leading cause of ESRD in children and young adults in the United States (1), a national database does not yet exist for glomerular diseases. Recent collaborations such as the Nephrotic Syndrome Study Network (2) are making progress toward this goal. The majority of studies describing the frequencies of glomerular diseases worldwide have typically been limited to specific disease entities and make use of data collected from multiple national registries. The data, however, may not always be comparable because of the lack of a common registry format (3). Add to this the relative infrequency of glomerular diseases, and it becomes clear why larger scale studies of their incidence are somewhat lacking. In this issue of the *Clinical Journal of the American Society of Nephrology*, O'Shaughnessy *et al.* (4) tackle this issue with a large-scale, single-center analysis of glomerular diseases spanning three decades (1986–2015).

The referral population for this study reflected a sizeable part of the southeastern United States, and this is the first large-scale study of glomerular diseases reported in this geographic area. In the United States, smaller scale studies have been reported from a single county in Minnesota (5), a recent study from southern Arizona (6) and a regional study of southern California through the Kaiser Permanente Health Care system (7). Although the relative ranking order varies, the most frequent glomerular diseases in all studies included FSGS and membranous nephropathy. FSGS was the most prevalent glomerular disease in southern Arizona, southern California, and the southeastern United States (4,6,7). IgA nephropathy was well represented in southern California and southern Arizona (6,7), likely representative of the reportedly larger Asian and Hispanic patient cohorts. However, IgA nephropathy was also the most common glomerular disease reported in predominantly white Olmstead County in Minnesota (5), and the fourth most common glomerular disease in the southeastern United States, where Asians and Hispanics made up only 4.2% of the cohort (4). Overall, however, the prevalence of the most common glomerular diseases does not appear to differ markedly between regional studies within the United States.

A notable difference between the study of O'Shaughnessy *et al.* (4) and other studies, however, is the inclusion of diabetic glomerulosclerosis (DG) as a glomerular disease entity; DG has largely been ignored in other United States and global studies of glomerular disease incidence. The results from this analysis are striking, in that the incidence of DG in the authors' patient population increased nearly four-fold over the study period across different ages (excluding the pediatric group), from 5.5% to 19.1%, mirroring national data showing an increase from 6.6% to 22.0% over a similar time period (8). DG also increased in relative frequency among nephrotic glomerular disease subtypes, rising from the fourth most common from 1986 to 1995 to the third most common from 1996 to 2005, and ultimately becoming the second most frequent nephrotic glomerular disease (the first being FSGS) during the period 2006–2015 (4).

These findings are particularly timely, given the increasing global and national prevalence of diabetes mellitus (DM). According to the World Health Organization, the prevalence of DM worldwide is 8.5% among adults over the age of 18 years, having risen from 4.7% in 1980 (9). In the United States, the prevalence of DM has been reported to be as high as 14.3% (10). Additionally, approximately 20%–40% of patients with diabetes have CKD (11). According to the American Diabetes Association, the total estimated cost of diagnosed diabetes in the United States in 2012 was $245 billion, and a recent study estimated the cost of CKD in adults with diabetes nationwide to be in excess of $43 billion in 2011 (12). These findings highlight the economic and health care burden of the increasing prevalence of DM and diabetes-related CKD.

Diabetic kidney disease (DKD) remains the leading cause of ESRD worldwide. In the United States, the prevalence of DKD showed a 1.5-fold increase from 1988 to 2008 (11), almost proportional to the nearly two-fold increase in the overall prevalence of DM in the general United States population during a similar interval (13) and to the increase in the prevalence of ESRD due to DKD from 1996 to 2014 reported by the USRDS (1). The nearly

four-fold increase in the renal biopsy frequency of DG in the study of O'Shaughnessy et al. (4) from 1986 to 2015 is at the very least in line with these changes. Any additional increment in the frequency of DG may be because DKD is a clinical diagnosis, traditionally made on the basis of the presence of albuminuria and/or impaired renal function. It is possible that histologic changes of DG may precede development of clinically manifest changes, and therefore may be underrepresented in studies of DKD.

Paradoxically, however, the yearly incidence (i.e., development of new cases) of ESRD among patients with DKD peaked in 2001 and has slowly declined over the past decade (1). Early diagnosis and intervention, with subsequent delay in the natural progression of disease toward ESRD, may be contributing to this trend. A decrease in smoking rates may also be a contributing factor toward slower rates of progression of DKD; the association of smoking with an increased rate of progression of DKD (14) is of particular interest because chronic smoking appears to produce renal histologic changes (increased mesangial matrix and nodular glomerulosclerosis) that mimic DG (15–17).

Risk factors for DKD can be subdivided into nonmodifiable and modifiable categories (18). Nonmodifiable risk factors include race, sex, age, and duration of DM. Traditional modifiable risk factors include glycemic control, hypertension, smoking, and physical activity. As a demographic study, the analysis of O'Shaughnessy et al. (4) focused primarily on nonmodifiable risk factors, with analysis of glomerular disease frequency within demographic subgroups as well as across age categories stratified by patient sex and race. The consistent increase in DG frequency across all adult age, sex, and racial groups was striking, and suggests that modifiable factors are primarily responsible for this increase.

Although the majority of the DG patients from this study likely represent type 2 DM, the precise breakdown between type 1 and type 2 DM is unclear, and thus it is unknown if the data from this study are similar to those seen nationwide. Because type 1 DM is much less common than type 2, much of the published data does not typically provide a statistical breakdown by diabetes type, and studies reporting the incidence of type 1 DM in the United States are quite rare. In one study, type 1 DM was reported to represent 4.6%–6.0% of all patients diagnosed with diabetes in the United States from 1999 to 2010 (19), with an increase in prevalence of 0.08% per 4-year interval during that time period. This increase in type 1 diabetes also parallels global trends in the 20th century, with a reported increase of 3% per year (20). Possible causes for this increase are the subject of much debate, with theories ranging from decreased "natural selection" (21) to a decrease in reportedly protective infections, to an increase in the incidence of viral infections that are thought to trigger autoimmunity (22). Given the role that environmental risk factors are thought to play, extrapolation of data from this study could potentially improve our understanding of the environmental determinants of type 1 DM in this regional patient population.

The study of O'Shaughnessy et al. (4) is also notable for inclusion of pediatric (0–17 years) patients, which is timely given the increasing rate of childhood obesity. Although DG in this age group was rare and did not increase over the study interval, a recent study of children (aged <18 years) in the

United States showed that the annual prevalence of type 1 DM increased from 1.48 to 2.32 per 1000 from 2002 to 2013, and the annual prevalence of type 2 DM increased from 0.38 to 0.67 per 1000 during the same interval (23). The increased prevalence of type 1 over type 2 DM is not unexpected, given that the former accounts for the majority of childhood and adolescent diabetes. However, several studies have shown that the incidence of type 2 DM is indeed increasing in this age group, in part because of childhood obesity, and that it disproportionately affects minority race/ethnic groups. In fact, it is estimated that 45% of pediatric and adolescent patients with newly diagnosed diabetes will have type 2 DM (24). This has profound implications, as in a study of 1856 Pima Indians with type 2 DM, the age- and sex-adjusted incidence of ESRD due to DKD in patients with DM onset before age 20 years (youth-onset type 2 DM) was nearly five-fold greater than in patients with onset between ages 20 and 55 years (adult-onset type 2 DM) (25). Furthermore, the death rate in individuals with youth-onset type 2 DM was double that of patients with adult-onset type 2 DM and triple that of nondiabetic study participants. Taken together, the findings of O'Shaughnessy et al. (4) regarding the marked increase in the incidence of DG over three decades in a large study of renal biopsy specimens, plus the vast body of epidemiologic evidence supporting the growing impact of DKD on public health and health care consumption and spending in the United States and worldwide, cry out for more concentrated efforts directed at prevention of DM, particularly type 2, plus screening and early intervention programs to prevent development of DKD in individuals identified to be at risk.

Disclosures
None.

References

1. United States Renal Data System: *2016 USRDS Annual Data Report: Epidemiology of Kidney Disease in the United States*, Bethesda, MD, National Institutes of Health, National Institute of Diabetes and Dnd Kidney Diseases, 2016
2. Gadegbeku CA, Gipson DS, Holzman LB, Ojo AO, Song PX, Barisoni L, Sampson MG, Kopp JB, Lemley KV, Nelson PJ, Lienczewski CC, Adler SG, Appel GB, Cattran DC, Choi MJ, Contreras G, Dell KM, Fervenza FC, Gibson KL, Greenbaum LA, Hernandez JD, Hewitt SM, Hingorani SR, Hladunewich M, Hogan MC, Hogan SL, Kaskel FJ, Lieske JC, Meyers KE, Nachman PH, Nast CC, Neu AM, Reich HN, Sedor JR, Sethna CB, Trachtman H, Tuttle KR, Zhdanova O, Zilleruelo GE, Kretzler M: Design of the Nephrotic Syndrome Study Network (NEPTUNE) to evaluate primary glomerular nephropathy by a multidisciplinary approach. *Kidney Int* 83: 749–756, 2013
3. Pesce F, Schena FP: Worldwide distribution of glomerular diseases: The role of renal biopsy registries. *Nephrol Dial Transplant* 25: 334–336, 2010
4. O'Shaughnessy M, Hogan S, Poulton C, et al: Temporal and demographic trends in glomerular disease epidemiology in the Southeastern United States, 1986–2015. *Clin J Am Soc Nephrol*, 12: 614–623, 2017
5. Swaminathan S, Leung N, Lager DJ, Melton 3rd LJ, Bergstralh EJ, Rohlinger A, Fervenza FC: Changing incidence of glomerular disease in Olmsted County, Minnesota: A 30-year renal biopsy study. *Clin J Am Soc Nephrol* 1: 483–487, 2006
6. Murugapandian S, Mansour I, Hudeeb M, Hamed K, Hammode E, Bijin B, Daheshpour S, Thajudeen B, Kadambi P: Epidemiology of glomerular disease in southern Arizona: Review of 10-year renal biopsy data. *Medicine (Baltimore)* 95: e3633, 2016
7. Sim JJ, Batech M, Hever A, Harrison TN, Avelar T, Kanter MH, Jacobsen SJ: Distribution of biopsy-proven presumed primary

glomerulonephropathies in 2000-2011 among a racially and ethnically diverse US population. *Am J Kidney Dis* 68: 533–544, 2016

8. Centers for Disease Control: Long term trends in diabetes. CDC National and State Data, 2016. Available at: https://www.cdc.gov/diabetes/data/. Accessed February 27, 2017

9. World Health Organization: Global report on diabetes, 2016. Geneva, Switzerland. Available at: http://www.who.int/diabetes/en/. Accessed February 27, 2017

10. Menke A, Casagrande S, Geiss L, Cowie CC: Prevalence of and trends in diabetes among adults in the United States, 1988-2012. *JAMA* 314: 1021–1029, 2015

11. de Boer IH, Rue TC, Hall YN, Heagerty PJ, Weiss NS, Himmelfarb J: Temporal trends in the prevalence of diabetic kidney disease in the United States. *JAMA* 305: 2532–2539, 2011

12. Ozieh MN, Dismuke CE, Lynch CP, Egede LE: Medical care expenditures associated with chronic kidney disease in adults with diabetes: United States 2011. *Diabetes Res Clin Pract* 109: 185–190, 2015

13. Centers for Disease Control and Prevention (CDC): Increasing prevalence of diagnosed diabetes–United States and Puerto Rico, 1995-2010. *MMWR Morb Mortal Wkly Rep* 61: 918–921, 2012

14. Feodoroff M, Harjutsalo V, Forsblom C, Thorn L, Wadén J, Tolonen N, Lithovius R, Groop PH: Smoking and progression of diabetic nephropathy in patients with type 1 diabetes. *Acta Diabetol* 53: 525–533, 2016

15. Markowitz GS, Lin J, Valeri AM, Avila C, Nasr SH, D'Agati VD: Idiopathic nodular glomerulosclerosis is a distinct clinicopathologic entity linked to hypertension and smoking. *Hum Pathol* 33: 826–835, 2002

16. Nasr SH, D'Agati VD: Nodular glomerulosclerosis in the nondiabetic smoker. *J Am Soc Nephrol* 18: 2032–2036, 2007

17. Salvatore SP, Troxell ML, Hecox D, Sperling KR, Seshan SV: Smoking-related glomerulopathy: Expanding the morphologic spectrum. *Am J Nephrol* 41: 66–72, 2015

18. Harjutsalo V, Groop PH: Epidemiology and risk factors for diabetic kidney disease. *Adv Chronic Kidney Dis* 21: 260–266, 2014

19. Menke A, Orchard TJ, Imperatore G, Bullard KM, Mayer-Davis E, Cowie CC: The prevalence of type 1 diabetes in the United States. *Epidemiology* 24: 773–774, 2013

20. Onkamo P, Väänänen S, Karvonen M, Tuomilehto J: Worldwide increase in incidence of type I diabetes–The analysis of the data on published incidence trends. *Diabetologia* 42: 1395–1403, 1999

21. You WP, Henneberg M: Type 1 diabetes prevalence increasing globally and regionally: The role of natural selection and life expectancy at birth. *BMJ Open Diabetes Res Care* 4: e000161, 2016

22. Egro FM: Why is type 1 diabetes increasing? *J Mol Endocrinol* 51: R1–R13, 2013

23. Li L, Jick S, Breitenstein S, Michel A: Prevalence of diabetes and diabetic nephropathy in a large U.S. commercially insured pediatric population, 2002-2013. *Diabetes Care* 39: 278–284, 2016

24. Craig ME, Jefferies C, Dabelea D, Balde N, Seth A, Donaghue KC; International Society for Pediatric and Adolescent Diabetes: ISPAD clinical practice consensus guidelines 2014. Definition, epidemiology, and classification of diabetes in children and adolescents. *Pediatr Diabetes* 15[Suppl 20]: 4–17, 2014

25. Pavkov ME, Bennett PH, Knowler WC, Krakoff J, Sievers ML, Nelson RG: Effect of youth-onset type 2 diabetes mellitus on incidence of end-stage renal disease and mortality in young and middle-aged Pima Indians. *JAMA* 296: 421–426, 2006