Glomerular Diseases in Patients with Diabetes Mellitus: An Underappreciated Epidemic

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The prevalence of non-diabetic kidney disease (NDKD) in patients with diabetes reflects the rising incidence of diabetes in the general population. The most current national prevalence of diabetes in US adults is at a high of 12.2%. A contributing factor is the obesity epidemic, as 87.5% of diabetic adults are overweight or obese. It is well known that chronic kidney disease (CKD) and end-stage kidney disease (ESKD) cause significant morbidity and mortality in obese and diabetic populations, with an estimated 36.5% of diabetics experiencing CKD (1). The relative risk of ESKD is higher in diabetics, ranging from 6.2 in white populations to 62.0 in Native Americans; of patients who start renal replacement therapy, 51% are estimated to have diabetes (2).

The diagnosis of diabetic kidney disease (DKD) is most often made clinically. However, there is growing awareness of the prevalence of NDKD with or without concomitant diabetic nephropathy (DN) in patients with diabetes. In turn, a large proportion of NDKD found on kidney biopsies are glomerular diseases. This knowledge draws attention to the possibility of undiagnosed, potentially reversible lesions in this population. Here, we review the prevalence and presentation of NDKD in diabetic patients, with a focus on glomerular lesions, and discuss the ways in which diabetes can affect the diagnosis and management of these conditions.

A review of native kidney biopsies for evidence of NDKD in diabetics performed at the Columbia Renal Pathology Laboratory in 2011 estimated that 23.5% of patients with native kidney biopsies carry a diagnosis of diabetes, roughly double the prevalence of diabetes in US adults. Of those patients, 37% had DN alone, 36% had NDKD alone, and 27% had concomitant DN and NDKD (3). A retrospective examination of renal biopsies at the Southern California Permanente Medical Group between 1995-2005 found a larger proportion of patients with NDKD alone (53.2%) or DN alone (27.5%) and fewer with both DN and NDKD (19.3%) (4). Both studies cited FSGS as the most common pathology in the NDKD alone group at 22% and 21%, respectively, followed by hypertensive nephrosclerosis, acute tubular
necrosis, IgA nephropathy, and membranous nephropathy (MN). Acute tubular necrosis was the most common diagnosis in the DN plus NDKD group in the Columbia cohort, whereas IgA nephropathy was most common in the California cohort (3, 4). It has been estimated that NDKD causes 40-60% of ESKD in patients with type 2 diabetes, while only 2-3% of renal disease in type 1 diabetics is of non-diabetic etiology (5).

Diabetic patients with glomerular disease represent a sizable patient population that, unfortunately, has been excluded from or under-enrolled in many recent clinical trials investigating management of glomerular diseases. The MENTOR trial, a randomized control trial published in 2019 that found rituximab to be non-inferior to cyclosporine in treating MN, excluded patients with type 1 and type 2 diabetes (6). The DUET trial, a 2018 trial proving the efficacy and safety of sparsentan in FSGS patients only included well-controlled type 2 diabetics and did not stratify subgroups by diabetes status (7). Similarly, the STOP-IgAN trial, a 2015 randomized control trial comparing immunosuppressive therapy to supportive care in IgA nephropathy, excluded patients with “other chronic renal diseases” without explicit mention of diabetes status (8). The TESTING trial, a 2017 randomized control trial comparing methylprednisolone to placebo for management of IgA nephropathy, did not exclude diabetic patients, yet there was only one patient with diabetes in the treatment group (0.7%) and three in the control group (2.4%) (9).

The exclusion of diabetic patients from these trials is predicated on the assumption that the presence of diabetes alters the natural history of primary glomerular diseases. The Cure Glomerulopathy Network (CureGN), an ongoing multi-center prospective observational study of patients with FSGS, MN, IgA nephropathy, and minimal change disease that characterizes the clinical and histopathological presentation and long-term outcomes of these diseases, also excludes patients with a history of diabetes at the time of first biopsy (10). We analyzed diabetic patients with FSGS and MN who were
excluded from CureGN at our site due to glycemic status but were otherwise eligible for participation. Of these patients, only 8.3% had type 1 diabetes. We compared these patients to an age-matched control group from our CureGN participants and found that kidney function at presentation was comparable in all groups. However, diabetic subjects in both disease groups had higher levels of proteinuria than controls, though only the MN group achieved statistical significance (Table 1). The lower-than-expected rate of anti-PLA2R positivity in the MN lesions seen in our diabetic subjects may suggest a positive titer as a potential marker for NDKD given its sensitivity and specificity idiopathic MN, though it does not account for the increased rate of secondary MN, the etiology of which remains unclear. Conceivably, the age and disease burden of diabetic patients could increase the rate of malignancy-associated cases of MN in our cohort, although we do not have detailed information on cancer screening to adjudicate that etiology. Patients with concurrent MN and DN on biopsy had reduced eGFR (48.0 vs 70.8 mL/min/1.73m²) and greater tubulointerstitial fibrosis (25.3% vs 6.3%) than those with MN alone, though this was not seen with FSGS.

Furthermore, the presence of DN in our cohort was associated with a higher rate of progression to ESKD regardless of diagnosis. Our data aligns with a 2011 retrospective study by Chang et al. that showed significantly worse cumulative renal survival in patients with DN alone versus either NDKD alone or concomitant disease, suggesting potential prognostic value of biopsy in cases with clinical suspicion for NDKD. The authors noted that nearly half of the patients with NDKD were treated with immunosuppression, mostly prednisolone, with a 67.6% complete or partial remission rate of both proteinuria and renal failure (11). While biopsy is not indicated in the diagnosis of DKD, these findings suggest there is a significant proportion of diabetic patients with NDKD for whom biopsy may not only aid in prognosis but also change disease management.
While indications for biopsy such as absence of retinopathy, diabetes duration <5 years, and microhematuria have been validated in type 1 diabetics, in whom the prevalence of NDKD is only 2-3%, evidence regarding biopsy criteria for type 2 diabetics is largely retrospective (5, 11). Factors most commonly identified in the literature include younger age, shorter duration of diabetes, higher hemoglobin levels, absence of retinopathy, and sudden onset of proteinuria (3, 4, 11, 12). Of these parameters, diabetic retinopathy had the highest sensitivity and specificity for DN (87% and 93%, respectively) (12). Duration of diabetes <5 years was most predictive of NDKD (75% sensitivity and 70% specificity), while duration ≥12 years had 53% sensitivity and 73% specificity for DN alone, with a decreased odds ratio of NDKD of 5% per each additional year of diabetes duration (3, 12). While none of these factors are diagnostic, presence of one or more can raise suspicion for NDKD and prompt earlier consideration of biopsy in diabetic patients.

Unfortunately, little evidence exists to guide management of primary glomerular diseases in diabetic patients due to underrepresentation in cohorts (retrospective and prospective) and clinical trials of glomerular disease. Glucocorticoids, the mainstay of primary glomerular disease management, carry a high morbidity profile as exemplified in the TESTING and STOP-IgAN trials; many of the toxicities of glucocorticoids, including hyperglycemia and weight gain, are expected to be worse in patients with comorbid diabetes (8, 9). Steroid-sparing immunosuppressive agents, including calcineurin inhibitors and rituximab, have proven effective alternatives for treating primary glomerular diseases and may be preferred in diabetic patients, although this strategy is based on clinical judgement rather than empiric data given the exclusion of diabetics from most trials (6, 13). Finally, canagliflozin, a sodium-glucose cotransporter 2 inhibitor, was recently approved by the FDA for use in patients with diabetes and DN on the basis of the CREDENCE trial, which showed a 34% reduction in a composite outcome of ESKD, doubling of creatinine, or renal or cardiovascular death. This could be an effective adjunctive therapy for diabetic patients with glomerular diseases, especially in those with concomitant DN (14).
In patients with type 2 diabetes and an atypical presentation of kidney disease, over 60% are likely to have NDKD with or without DN (3, 4). Additionally, diabetic patients with NDKD have greater renal survival compared to those with DN alone. Thus, consideration of kidney biopsy to make a diagnosis and potentially guide treatment for reversible lesions is an important component of evaluating diabetic patients. Indeed, a culture change appears necessary to address what is an underappreciated and growing epidemic of NDKD. Fortunately, ongoing observational studies are examining the role of biopsy in diabetic patients with kidney dysfunction, including the NIDDK-sponsored Kidney Precision Medicine Project (KPMP) and the TRIDENT study, both of which will examine blood, urine, tissue, and genetic markers in diabetic patients in order to elucidate molecular pathways of disease (15).

There still exists a need to enroll diabetic patients with glomerular diseases in observational studies of glomerular diseases as well as in clinical trials of disease-targeting agents. The exclusion of diabetic patients from these studies not only underrepresents a growing population of patients with higher morbidity and mortality but also creates a significant healthcare disparity given higher rates of diabetes among African Americans and Latinos compared to whites. The nephrology community has clearly recognized the role of DKD in the epidemics of CKD and ESKD. Now is the time for us to recognize the role of NDKD, particularly glomerular lesions, so that we can begin to address a heretofore underappreciated epidemic.
Disclosures

PAC and ASB are co-investigators for the Columbia University site of the Cure Glomerulopathy (CureGN) study. ASB is a principal investigator and PAC is a co-investigator for the Columbia University site of the Kidney Precision Medicine Project (KPMP) study. The authors have nothing else to disclose.

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Author Contributions

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Table 1. Clinical characteristics of sampled diabetic and non-diabetic patients with (A) Focal Segmental Glomerulosclerosis and (B) Membranous Nephropathy at the Center for Glomerular Diseases of Columbia University.

|                  | Diabetic cohort | Age-matched CureGN controls | p-value |
|------------------|-----------------|-----------------------------|---------|
| **(A) FSGS, n=** | 22              | 44                          |         |
| Age at first biopsy (y) | 60.0 ± 11.7     | 59.5 ± 11.8                 | 0.9     |
| Serum creatinine (mmol/L) | 2.54 ± 2.85     | 1.94 ± 0.97                 | 0.2     |
| eGFR (mL/min/1.73m²) | 47.0 ± 36.2*    | 41.5 ± 19.9*                | 0.4     |
| Proteinuria (g/g or g/day) | 7.1 ± 4.6      | 5.0 ± 4.4                   | 0.09    |
| **(B) MN, n=**   | 26              | 52                          |         |
| Age at first biopsy (y) | 61.3 ± 11.1     | 61.3 ± 11.1                 | 1.0     |
| Serum creatinine (mmol/L) | 1.35 ± 0.68     | 1.39 ± 0.78                 | 0.8     |
| eGFR (mL/min/1.73m²) | 62.0 ± 29.4     | 63.2 ± 31.5                 | 0.9     |
| Proteinuria (g/g or g/day) | 10.3 ± 7.8     | 7.2 ± 5.8                   | 0.03    |
| Hematuria (dipstick), n (%) |                  |                             | 0.005   |
| None/trace       | 11 (43.2)       | 30 (57.7)                   |         |
| 1+               | 3 (11.5)        | 10 (19.2)                   |         |
| 2+               | 6 (23.1)        | 4 (7.7)                     |         |
| 3+               | 6 (23.1)        | 3 (5.8)                     |         |
| Unknown          | 0               | 5 (9.6)                     |         |
| Anti-PLA2R Variant, n (%) |             |                             | 0.01    |
| Positive         | 10 (38.5)       | 28 (53.8)                   |         |
| Negative         | 13 (50.0)       | 11 (21.2)                   |         |
| Unknown          | 3 (11.5)        | 13 (25.0)                   |         |

* Differences in eGFR attributed to 23% African American representation in diabetic cohort versus 14% in the control group. FSGS = focal segmental glomerulosclerosis; MN = membranous nephropathy.