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Glomerular Diseases in Patients with Diabetes Mellitus: An Underappreciated Epidemic

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Introduction

The prevalence of nondiabetic 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 United States 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 CKD and 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 RRT, 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 is 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 United States 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 and 2005 found larger proportions 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, whereas only 2%–3% of renal disease in type 1 diabetics is of nondiabetic etiology (5).

Diabetic patients with glomerular disease represent a sizable patient population that, unfortunately, has been excluded from or underenrolled 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 noninferior to cyclosporin 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 patients with FSGS 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 with 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 with 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 multicenter, prospective, observational study of patients with FSGS, MN, IgA nephropathy, and minimal change disease that characterizes the clinical and histopathologic 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 the 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 with 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, although only the MN group achieved statistical significance (Table 1). There was a lower than

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expected rate of anti-PLA2R positivity in the MN lesions seen in our diabetic subjects. Given the high sensitivity and specificity of the anti-PLA2R titer for idiopathic MN, this may suggest a positive titer as a potential marker for NDKD. However, this explanation does not account for the increased rate of secondary MN; 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 versus 70.8 ml/min per 1.73 m^2) and greater tubulointerstitial fibrosis (25.3% versus 6.3%) than those with MN alone, although 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 align with a 2011 retrospective study by Chang *et al.* (11) 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). Although biopsy is not indicated in the diagnosis of DKD, these findings suggest that there is a significant proportion of diabetic patients with NDKD for whom biopsy may not only aid in prognosis but also, change disease management.

Table 1. Clinical characteristics of sampled diabetic and nondiabetic patients with FSGS and membranous nephropathy at the Center for Glomerular Diseases of Columbia University

Characteristics	Diabetic Cohort	Age-Matched CureGN Controls	*P* Value
FSGS, *n*	22	44	
Age at first biopsy, yr	60.0±11.7	59.5±11.8	0.90
Serum creatinine, mmol/L	2.54±2.85	1.94±0.97	0.20
eGFR, ml/min per 1.73 m^2	47.0±36.2[a]	41.5±19.9[a]	0.40
Proteinuria, g/g or g/d	7.1±4.6	5.0±4.4	0.09
MN, *n*	26	52	
Age at first biopsy, yr	61.3±11.1	61.3±11.1	>0.99
Serum creatinine, mmol/L	1.35±0.68	1.39±0.78	0.80
eGFR, ml/min per 1.73 m^2	62.0±29.4	63.2±31.5	0.90
Proteinuria, g/g or g/d	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)	

CureGN, Cure Glomerulopathy Network; MN, membranous nephropathy; PLA2R, phospholipase A2 receptor.
[a]Differences in eGFR attributed to 23% black representation in the diabetic cohort versus 14% black representation in the control group.

Although 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), whereas 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). Although 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 under-representation 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 to be effective alternatives for treating primary glomerular diseases, and they may be preferred in diabetic patients, although this strategy is on the basis of clinical judgement rather than empirical data given the exclusion of diabetics from most trials (6,13). Finally, canagliflozin, a sodium-glucose cotransporter 2 inhibitor, was recently approved by the Food and Drug Administration 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, >60% are likely to have NDKD with or without DN (3,4). Additionally, diabetic patients with NDKD have greater renal survival compared with 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 seems 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 National Institute of Diabetes and Digestive and Kidney Diseases–sponsored Kidney Precision Medicine Project and the TRIDENT study, both of which will examine blood, urine, tissue, and genetic markers in diabetic patients 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 under-represents a growing population of patients with higher morbidity and mortality but also, creates a significant health care disparity given higher rates of diabetes among blacks and Latinos compared with 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.

Author Contributions

A. Bomback conceptualized the study, was responsible for methodology, supervised the study, and reviewed and edited the manuscript; P. Canetta provided supervision and reviewed and edited the manuscript; and N. Freeman was responsible for data curation and formal analysis as well as investigation and methodology, wrote the original draft of the manuscript, and reviewed and edited the manuscript.

Disclosures

A. Bomback and P. Canetta are coinvestigators for the Columbia University site of the Cure Glomerulopathy study. A. Bomback is a principal investigator and P. Canetta is a coinvestigator for the Columbia University site of the Kidney Precision Medicine Project study. N. Freeman has nothing to disclose.

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