Kidney Biopsy Findings Among Patients With Diabetes in the Cleveland Clinic Kidney Biopsy Epidemiology Project

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Rationale & Objectives: Diabetic kidney disease (DKD) is a significant complication of diabetes mellitus, often leading to kidney failure. The absence of well-defined factors prevents distinguishing DKD from non-diabetic kidney disease (non-DKD; alternative primary diagnosis identified on kidney biopsy).

Study Design: Retrospective cohort study.

Setting & Participants: This study assessed 1,242 patients with a history of diabetes from the Cleveland Clinic Kidney Biopsy Epidemiology Project between January 2015 and September 2021.

Exposure: Proteinuria, retinopathy, A1c levels, and estimated glomerular filtration rate.

Outcomes: Non-DKD, defined as an alternative primary diagnosis identified on kidney biopsy other than DKD.

Analytical Approach: Multivariate logistic regression model with backward elimination method.

Results: At the time of biopsy, the median (IQR) age was 63 (53-71 years) years, and 58.8% were men. The median hemoglobin A1c value was 6.7% (6.0%-8.1%), and the median serum creatinine level was 2.5 (1.6-3.9 mg/dL) mg/dL. Among 1,242 patients, 462 (37.2%) had DKD alone, and 780 (62.8%) had non-DKD. Among those with non-DKD, the most common diagnoses were focal segmental glomerulosclerosis (24%), global glomerulosclerosis otherwise not specified (13%), acute tubular necrosis (9%), IgA nephropathy (8%), antineutrophil cytoplasmic antibody vasculitis (7%), and membranous nephropathy (5%). Factors associated with having non-DKD on biopsy were having no retinopathy (vs retinopathy) (adjusted odds ratio [aOR], 3.98; 95% CI, 2.69-5.90), lower A1c levels (<7% vs ≥7%) (aOR, 3.08; 95% CI, 2.16-4.39), higher estimated glomerular filtration rate (≥60 vs <60 mL/min/1.73 m^2) (aOR, 2.39; 95% CI 1.28-4.45), microalbuminuria (<300 vs macroalbuminuria ≥300 [mg/g]) (aOR; 2.94; 95% CI, 1.84-4.72), and lower protein-creatinine ratio on random urine sample (<3 vs ≥3 mg/mg) (aOR; 1.80; 95% CI, 1.24-2.61).

Limitations: Selection bias of clinically indicated biopsies, not protocol biopsies, which likely represent a ceiling (maximum) for non-DKD.

Conclusions: Among patients with diabetes undergoing kidney biopsy, 63% have findings in addition to DKD on biopsy. We identified clinical parameters associated with non-DKD in the setting of diabetes. This provides valuable information for clinicians when kidney biopsy should be considered among patients with diabetes to capture all etiologies of proteinuria and kidney dysfunction.

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Patients with chronic disease (CKD) and diabetes mellitus, when confronted with persistent kidney dysfunction and/or proteinuria without clear causative factors, are frequently clinically diagnosed with diabetic kidney disease (DKD).[1,2] DKD is believed to be the predominant etiology of kidney failure, a phenomenon exacerbated by the increasing prevalence of type 2 diabetes in recent decades.[3,4] In 2021, the US Department of Health and Human Services showed that 44.2% of treated kidney failure cases were attributed to diabetes. It is worth noting that a significant proportion of kidney failure cases attributed to DKD were diagnosed without the confirmation of kidney biopsy. Although clinical judgment in this setting is key and continues to be standard practice, it is important for clinicians to know which factors ensure/prompt kidney biopsy in a patient with diabetes. Currently, factors such as rapidly declining kidney function, unusual clinical course, positive serology, systemic diseases or active urinary sediment prompt biopsy, but this is the practice for most kidney diseases. Additionally, there is a lack of data to guide the decision on kidney biopsy that is grounded in validated statistical models.[2,5-9]

In addition to the well-known associations of having diabetic retinopathy or other diabetes-related end organ damage with the likelihood of having DKD, the current data and epidemiologic reports have identified some factors associated with biopsy-proven DKD in patients with diabetes.[2,7,10,11] One study suggests that for each additional year of diabetes duration, the odds of having non-diabetic kidney disease decrease by 5%. Other studies suggest diabetes duration exceeding 5-12 years as being a strong predictor of DKD diagnosis.[2,10,12] Other potential markers, such as hemoglobin levels and serum D-serine levels, have also been explored to improve pre-kidney biopsy predictions for DKD or non-DKD, but a consensus is yet to be reached.[10,12,13]

Adding to the complexity, patients with diabetes may have DKD along with other concurrent actionable kidney

PLAIN-LANGUAGE SUMMARY

Our study aimed to better understand when to perform kidney biopsies in patients with diabetes. Often, nephrologists diagnose diabetes-related kidney disease based on clinical parameters without a biopsy. We sought to look at what the spectrum of kidney biopsy findings were in patients with a clinical history of diabetes to see how many patients had diabetic kidney disease or other findings. Given the advent of several new medications that treat and slow the progression of diabetic kidney disease, we also sought to see what clinical factors were more likely to suggest a finding of nondiabetic kidney disease on biopsy to help guide clinicians when to biopsy in this population.

conditions, which may remain undetected without a kidney biopsy. Previous cohorts have demonstrated that among patients with diabetes, a significant percentage (ranging from 22%-64%) exhibited non-DKD.[2,7,9-11,14] Given that patients clinically diagnosed with diabetes, in the absence of other compelling criteria for kidney biopsy, are often managed as if they have DKD, our study aimed to provide insight into the spectrum of kidney biopsy findings among patients with diabetes, to demonstrate how many patients with diabetes have DKD or non-DKD (with or without superimposed DKD). Additionally, we sought to identify factors associated with the diagnosis of non-DKD within this specific patient population to help guide clinical decision making on when to strongly consider kidney biopsy, especially given the advent of new therapies to slow its progression and decrease the worldwide burden of DKD related CKD and kidney failure.

METHODS

Study Design

This retrospective study was approved with waiver of consent by the Cleveland Clinic, Institutional Review Board (IRB# 22-819). Our patient cohort was drawn from the Cleveland Clinic Kidney Biopsy Epidemiology Project (CCKBEP). The CCKBEP is a catalog of the biopsy diagnoses as well as clinical and demographic data of all patients who had a kidney biopsy performed/reviewed at the Cleveland Clinic from January 2015 to September 2021.[15] Using this population, we first identified patients with *International Classification of Diseases, Tenth revision* (ICD-10) code data available in the electronic medical record (EMR) and then identified those who had ICD-10 code consistent with diabetes.

All hospitals in our health care system use an interoperable EMR (EPIC, Epic Systems Corporation) and share a home-grown universal data warehouse repository called the Enterprise Data Vault (EDV). The health system's Enterprise Analytics Division developed EDV to make accessible to clinicians and information systems practitioners the clinical and laboratory information recorded in our EMR, as well as ICD-10 data. Queries were developed against our EDV, which resides in our Teradata (Teradata Corporation) database to obtain the data.

For the purposes of this study, any ICD-10 code containing E08 (diabetes mellitus because of underlying condition), E09 (drug- or chemical-induced diabetes mellitus), E10 (type 1 diabetes mellitus), E11 (type 2 diabetes mellitus), and E13 (other specified diabetes mellitus) for each patient was captured. If this was present, the patient was determined to have a history of diabetes. The result was more than 24,000 instances of one or more than one of these codes present among more than 3,500 patients. This strategy was implemented to maximize capture of patients with diabetes because it is often under coded in the EMR.

Clinical Parameters

After identifying all patients with a kidney biopsy and ICD-10 code of diabetes in the CCKBEP, we abstracted clinical and laboratory data obtained within 90 days before the biopsy using queries from the EDV as described above. The following variables were queried and obtained: diagnoses of hypertension and retinopathy by ICD-10 codes, serum creatinine levels, estimated glomerular filtration rate (eGFR) calculated using the 2021 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, serum albumin levels, hemoglobin A1c levels, complement 3 (C3) levels, C4 levels, anti-nuclear antibody levels, anti-dsDNA antibody levels, anti-phospholipase A2 receptor (PLA2R) antibody levels, anti-neutrophilic cytoplasmic antibody (ANCA) serology for myeloperoxidase (MPO)/proteinase 3 (PR3), anti-glomerular basement membrane (GBM) antibody levels, hepatitis C serology, HIV status, and urinalysis at the time of biopsy, including proteinuria, hematuria, and proteinuria by either random urinary albumin-creatinine ratio (UACR), urinary protein-creatinine ratio (UPCR), or 24-hour urine collection. For the purposes of this study, hematuria was defined as a ≥3 red blood cells per high-powered field or detected as >small or >1+ on urinalysis. To help account for missing UACR data, UACR was calculated from UPCR using the CKD prognosis consortium models (sum albumin-creatinine ratio [ACR]). The variable, sum ACR, includes both measured and calculated UACR values combined.

Kidney Pathology

Each biopsy report underwent examination by a nephropathologist as part of clinical care affiliated with the Cleveland Clinic, following a standardized protocol encompassing procedures for light microscopy (using hematoxylin and eosin, periodic acid–Schiff, trichrome, and Jones stains) as well as immunofluorescence (involving IgG, IgA, IgM, C3, C1q, kappa, lambda, and albumin) and electron microscopy. We defined DKD as

diffuse mesangial sclerosis with GBM thickening, with or without mesangial nodularity on light microscopy. Additional features supportive of DKD included diffuse linear albumin and IgG on glomerular and tubular basement membranes, thickened tubular basement membranes (nonatrophic tubules), glomerular and arteriolar hyalinosis.

When additional diagnoses were present, the pathologist made an effort to indicate the relative contributions of DKD and non-DKD, indicating whenever possible whether DKD or non-DKD was the alternative primary diagnosis associated with the clinical presentation at the time of biopsy. As lesions such as global glomerulosclerosis are found in many different diseases, descriptive diagnoses such as global glomerulosclerosis otherwise not specified (NOS) were only used in cases for which a more specific diagnosis, such as DKD, was not evident. Finally, based on the primary diagnosis obtained, for the purposes of this study, these kidney biopsies were classified into distinct categories, namely DKD alone, DKD with superimposed non-DKD, and non-DKD alone, for reporting and analysis.

Statistical Analysis

Patient characteristics were presented using descriptive statistics including median (interquartile rage [IQR]) for continuous variables and percentages for categorical variables. χ^2 test or Fisher exact test when appropriate was used for analyzing categorical variables, whereas Wilcoxon rank-sum test was applied for continuous variables. In addition, a multivariate logistic regression model with backward elimination method was conducted to determine the independent factors for non-DKD. All statistical analyses were conducted using Stata version 16.1 (StataCorp).

RESULTS

Of 4,125 patients with native kidney biopsies in the CCKBEP, 3,500 had ICD-10 code data available. We identified 1,268 (36.2%) with an ICD-10 code for diabetes. Of these, 462 (36.4%) had DKD alone, and 675 (53.2%) had non-DKD alone. In addition, 105 (8.3%) had both DKD and non-DKD, and 26 (2.1%) were either normal or nondiagnostic (these patients were excluded from final analysis). Table 1 presents baseline characteristics of the 1,242 patients by biopsy result. Patients had a median (IQR) age of 63 (53-71 years) years, and 58.8% were men. In total, 66.3% were White, and 93.7% had hypertension. The median hemoglobin A1c level was 6.7 (6.0%-8.1%), and 21.3% had retinopathy. The median serum albumin level was 3.4 (2.8-3.9 g/dL), and 46.5% had a serum albumin level ≥3.5 g/dL. The median serum creatinine level was 2.5 (1.6-3.9 mg/dL), and the median eGFR was 24.2 (14.9-42.0 mL/min/1.73 m^2) (calculated using the 2021 CKD-EPI creatinine equation). In addition, 86.4% had eGFR levels below 60 mL/min/1.73 m^2.

Immunochemistry and Laboratory Values

Table 1 also summarizes the serological and laboratory values of patients with diabetes when comparing non-DKD patients (regardless of accompanying DKD histopathology) to those with DKD alone. For univariate analysis, among non-DKD patients, 87.3% had detectable proteinuria (≥trace [10-30 mg/dL]) compared with 96.1% of DKD alone patients (P value < 0.001). The median (IQR) urine protein to creatinine ratio among non-DKD patients was 2.1 (0.8-5.1 mg/mg) mg/mg. In DKD alone patients, it was 4.4 (1.9-7.4 mg/mg) mg/mg, which was statistically different (P value < 0.001). Random UACRs were statistically different between the non-DKD group (median, 478; IQR, 59-1,906 mg/g) and the DKD alone group (1,462; 447-2,975 mg/g) with a P value of <0.001 (similar results for sum ACR). C3 levels showed statistical difference between groups (non-DKD: 120; 99-143 mg/dL vs DKD alone: 125; 107-143 mg/dL; P value = 0.05), and this was similar for C4 levels as well (non-DKD: 28; 21-35 mg/dL vs DKD alone 29; 23-37 mg/dL; P value = 0.006). When comparing the composite of serologic testing (antibodies to p-ANCA/MPO, c-ANCA/PR3, antinuclear, anti-dsDNA, anti-GBM, anti-PLA2R, hepatitis C, or abnormal free kappa/lambda ratio in serum), the non-DKD group had a positivity rate of 22.5%, whereas the DKD alone group had a rate of 10.7% (P value < 0.001).

Factors Associated with Non-DKD

Multivariable analysis (Table 2) showed factors associated with having non-DKD on biopsy were having no retinopathy (vs retinopathy) (adjusted odds ratio [aOR], 3.98; 95% confidence interval [CI], 2.69-5.90), lower A1c level (<7% vs ≥7%) (aOR, 3.08; 95% CI, 2.16-4.39), higher eGFR (≥60 vs <60 mL/min/1.73 m^2) (aOR, 2.39; 95% CI, 1.28-4.45), microalbuminuria (<300 vs macroalbuminuria ≥300 [mg/g]) (aOR; 2.94; 95% CI, 1.84-4.72), and lower UPCR (<3 vs ≥3 mg/mg) (aOR; 1.8; 95% CI, 1.24-2.61).

Kidney Biopsy Summary

Table 3 describes the baseline kidney biopsy summary of patients with diabetes by biopsy result (all non-DKD vs non-DKD alone vs non-DKD with DKD). The most common histopathology among non-DKD patients was focal segmental glomerulosclerosis (23.7%), followed by global glomerulosclerosis NOS (12.7%), acute tubular necrosis (ATN) (9.0%), IgA nephropathy (7.9%), ANCA vasculitis/pauci-immune glomerulonephritis (7.4%), membranous nephropathy (4.7%), postinfectious glomerulonephritis (PIGN) (4.6%), and others (Table 3). When comparing patients with non-DKD alone to those with DKD and concomitant non-DKD, statistically significant differences in prevalence were observed for global glomerulosclerosis

Table 1. Patient Characteristics of Patients With Diabetes in the CCKBEP by Biopsy Result

Variable	All (n=1,242)	Non-DKD (n=780)	DKD alone (n=462)	*P* value
Age, y	63 (53-71)	65 (55-72.5)	60 (50-68)	<0.001
Age, y				<0.001
18≤age≤50	240 (19.3)	124 (15.9)	116 (25.1)	
50<age≤60	298 (24.0)	178 (22.8)	120 (26.0)	
60<age≤70	379 (30.5)	236 (30.3)	143 (31.0)	
Age>70	325 (26.2)	242 (31.0)	83 (18.0)	
Sex (male)	730 (58.8)	473 (60.6)	257 (55.6)	0.08
Race (White)	823 (66.3)	546 (70.0)	277 (60.0)	<0.001
Hemoglobin A1c (%) (n=985)	6.7 (6.0-8.1)	6.4 (5.8-7.3) (n=594)	7.5 (6.5-9.0) (n=391)	<0.001
Hemoglobin A1c ≥7%	433 (44.0)	188 (31.7)	245 (62.7)	<0.001
Hypertension	1,164 (93.7)	720 (92.3)	444 (96.1)	0.008
Retinopathy	264 (21.3)	84 (10.8)	180 (39.0)	<0.001
Albumin, serum (g/dL) (n=1143)	3.4 (2.8-3.9)	3.4 (2.8-4.0) (n=724)	3.3 (2.8-3.7) (n=419)	0.001
Albumin ≥3.5g/dL, serum	532 (46.5)	361 (49.9)	171 (40.8)	0.003
Creatinine at biopsy, serum (mg/dL) (n=1,153)	2.5 (1.6-3.9)	2.5 (1.6-4.0) (n=623)	2.6 (1.7-3.5) (n=373)	0.55
eGFR (mL/min/1.73 m^2)[a] (n=1,153)	24.2 (14.9-42.0)	25.2 (13.9-43.8)	25.3 (16.4-42.5)	0.40
eGFR <60 mL/min/1.73 m^2	996 (86.4)	623 (85.2)	373 (88.4)	0.13
HIV 1/2, positive (n=132)	5 (3.8)	2 (2.3) (n=89)	3 (7.0) (n=43)	0.33
Hepatitis C, positive (n=145)	12 (8.3)	8 (9.5) (n=84)	4 (6.6) (n=61)	0.76
Protein, random urine output				<0.001
Negative (<10 mg/dL)	117 (9.4)	99 (12.7)	18 (3.9)	
Equal to trace (10-30 mg/dL) or more	1,125 (90.6)	681 (87.3)	444 (96.1)	
Hematuria, random urine output (n = 1,094)[b]	711 (65.0)	448 (64.6) (n=694)	263 (65.8) (n=400)	0.69
Protein to creatinine ratio, random urine output (mg/mg) (n=754)	3.0 (1.1-6.0)	2.1 (0.8-5.1) (n=459)	4.4 (1.9-7.4) (n=295)	<0.001
Protein to creatinine ratio ≥3 mg/mg	379 (50.3)	190 (41.4)	189 (64.1)	<0.001
Albumin to creatinine ratio, random urine output (mg/g) (n=562)	886 (115-2,443.6)	478 (59-1,906) (n=329)	1,462 (447-2,975) (n=233)	<0.001
Albumin to creatinine ratio ≥886 mg/g	282 (50.2)	135 (41.0)	147 (63.1)	<0.001
Sum ACR (mg/g) (n=890)	1,234 (238-3,037)	847 (128-2,451)	1970 (650-3,753)	<0.001
Sum ACR ≥ 300 mg/g	644 (72.4)	347 (64.0)	297 (85.3)	<0.001
Complement 3 (mg/dL) (n=784)	123 (102-143)	120 (99-143) (n=477)	125 (107-143) (n=307)	0.05
Complement 3 ≥123 mg/dL	394 (50.3)	225 (47.2)	169 (57.2)	0.03
Complement 4 (mg/dL) (n=7 23)	28 (22-36)	28 (21-35) (n=440)	29 (23-37) (n=283)	0.006
Complement 4 ≥28 mg/dL	387 (53.5)	225 (51.1)	162(57.2)	0.11
P-ANCA/MPO, positive (n=520)	68 (13.1)	55 (17.0) (n=324)	13 (6.6) (n=196)	<0.001
C-ANCA/PR3, positive (n=485)	29 (6.0)	24 (8.0) (n=302)	5 (2.7) (n=183)	0.02
Any positive serology (n=616)[c]	111 (18.0)	86 (22.5) (n=382)	25 (10.7) (n=234)	<0.001

Note: Median (IQR) or n (%).
Abbreviations: DKD, diabetic kidney disease; non-DKD, nondiabetic kidney disease; Sum ACR, Albumin to creatinine ratio calculated from protein to creatinine ratio via CKD consortium prognosis calculator and measured UACR.
[a]eGFR are calculated by use of the 2021 CKD-EPI creatinine equation.
[b]Defined as hematuria if random urine output meets any of the following conditions: hemoglobin ≥1+, hemoglobin ≥small, or ≥3 red blood cells per high-powered field.
[c]Antibodies to P-ANCA/MPO (n=510), C-ANCA/PR3 (n=475), anti-nuclear (n = 5), anti-dsDNA (n=37), anti-GBM (n=42), anti-phospholipase A2 receptor (n=4), Hepatitis C (n=145) positivity, or a serum free kappa/lambda ratio outside the reference range (n=13).

NOS (*P* value = 0.02), PIGN (*P* value = 0.001), and oxalate nephropathy (*P* value = 0.009) (Table 3).

DISCUSSION

In our study of 4,125 patients who underwent native kidney biopsies as part of the CCKBEP, 1,242 patients with diabetes had biopsy results that shed light on factors associated with non-DKD when compared with DKD alone. Key findings showed that 62.8% of patients with a clinical history of diabetes had findings in addition to DKD on kidney biopsy. Prior cohorts of native kidney biopsy among diabetes patients showed that 64% (n=371),[2] 63% (n=142),[14] 61% (n=321),[7] 48% (n=220),[9] 40% (n=302),[10] and 25% (n=160)[11] had either non-DKD alone or DKD with superimposed non-DKD. Our analysis identified lack of retinopathy, low hemoglobin A1c levels, higher eGFR, microalbuminuria (vs macroalbuminuria), and lower degree of UPCR as independently associated with non-DKD. These findings, in addition to the previously well-known conditions such as other diabetic end organ damage and duration of diabetes, aid clinicians in

Table 2. Factors Associated with non-DKD (n=780) Compared With DKD Alone (n=462) Among Patients With Diabetes in the CCKBEP (multivariable)[a]

Variables	Adjusted Odds Ratio	95% Confidence Interval	*P* Value
Hemoglobin A1c (%)			
≥7	Ref		
<7	3.08	(2.16-4.39)	<0.001
eGFR (mL/min/1.73 m^2)[b]			
<60 (ref)	Ref		
≥60	2.39	(1.28-4.45)	0.006
Sum ACR (mg/g)			
≥300	Ref		
<300	2.94	(1.84-4.72)	<0.001
Protein to creatinine ratio, random urine output (mg/mg)			
≥3	Ref		
<3	1.80	(1.24-2.61)	0.002
Retinopathy			
Yes	Ref		
No	3.98	(2.69-5.90)	<0.001

Abbreviations: DKD, diabetic kidney disease; non-DKD, nondiabetic kidney disease; Sum ACR, Albumin to creatinine ratio calculated from protein to creatinine ratio via CKD consortium prognosis calculator and measured UACR.
[a]Non-DKD from kidney biopsy regardless of DKD result.
[b]eGFR are calculated using the 2021 CKD-EPI creatinine equation. All variables in Table 1 except the variables with > 40% missing observations and hematuria with *P* value of 0.69 were included in the model as explanatory variables (age, sex, race, A1c, albumin, eGFR, protein, protein to creatinine ratio, retinopathy, hypertension, sum ACR, and complement 3), and finally protein (*P* = 0.34), albumin (*P* = 0.53), race (*P* = 0.60), complement 3 (*P* = 0.53), hypertension (*P* = 0.10), sex (*P* = 0.18), and age (*P* = 0.26) were eliminated using the backward elimination method.

predicting the presence of non-DKD among patients with diabetes, assisting with clinical decision making regarding kidney biopsy in this population. Because we live in an era with new therapeutic agents to slow the progression of DKD, such as sodium glucose cotransporter inhibitors and mineralocorticoid receptor antagonists, such as finerenone, it is essential we determine the presence or absence of DKD.

Interestingly, other major studies have reported membranous nephropathy (33%, n=302 and 17%, n=321), ATN (29%, n=101), or IgA nephropathy (13%, n=110) as the most common histopathologic diagnosis in non-DKD.[7,10,12,16] In contrast, our study found that focal segmental glomerulosclerosis (23%) was the most frequently observed biopsy result. This discrepancy could be attributed to different geographic variations in prevalence, as well as different demographic compositions.[2,7,10,12] Additionally, the prevalence of global glomerulosclerosis NOS, oxalate nephropathy, and PIGN differed between non-DKD alone versus when non-DKD was superimposed on DKD (Table 3), suggesting that in the presence of comorbid conditions, such as hypertension, obesity, infection, and oxalosis (and its associated risk factors), kidney biopsy in patients with diabetes should be considered.

In our study, we demonstrated that having lower levels or proteinuria, eg, microalbuminuria versus macroalbuminuria, was associated with finding non-DKD on kidney biopsy, compared with DKD. This association of lower proteinuria with non-DKD was further confirmed on multivariable analysis, with lower UPCR (<3 vs ≥3 mg/mg) (aOR; 1.8; 95% CI, 1.24-2.61) emerging as a significant factor associated with finding non-DKD. The role of proteinuria as an independent association factor for non-DKD has been a subject of debate, with previous studies showing inconsistent results.[2,7,10,12,17] Our study, benefiting from a rich dataset and a large study population, highlighted the association of lower UPCR with non-DKD. Clinically, this shows that one would expect patients with DKD to have more proteinuria, given it is typically classified as part of the nephrotic forms of glomerular disease compared with others such as IgA nephropathy, ATN, and ANCA vasculitis. Given that our study shows that lower proteinuria is associated with non-DKD, consideration needs to be made for biopsy if they have other predictors of non-DKD, such as rapid decline of kidney function or any positive serology, in the setting of a clinically lower degree of proteinuria in addition to other clinical indications of kidney biopsy.[18]

Although efforts were made to include serologic testing for systemic diseases such as autoimmune-related (antibodies to anti-nuclear, anti-dsDNA, C3, and C4) and viral antibodies (hepatitis B or hepatitis C), as well as monoclonal gammopathy (urine and serum protein electrophoresis), these factors by themselves did not show statistical significance with non-DKD, likely because of lack of testing/missing data given the retrospective nature of the study.[2] Our study showed a robust positive association of C3 levels (P value = 0.05), C4 levels (P value = 0.006), p-ANCA/MPO (P value < 0.001), and c-ANCA/PR3 (P value = 0.02) with non-DKD using univariate analysis. Given the incompleteness of serology, characterized by more than

Table 3. Kidney Biopsy Summary of Patients With Diabetes in CCKBEP by Biopsy Result[a]

Types of non-DKD	All non-DKD (n=780)	non-DKD Alone (n=675)	non-DKD with DKD (n=105)	*P* Value
Acute interstitial nephritis	22 (2.8)	20 (3.0)	2 (1.9)	0.76
Acute tubular necrosis	70 (9.0)	58 (8.6)	12 (11.4)	0.36
Amyloidosis	21 (2.7)	21 (3.1)	0 (0.0)	0.1
ANCA vasculitis/pauci-immune glomerulonephritis	58 (7.4)	49 (7.3)	9 (8.6)	0.55
Chronic interstitial nephritis	15 (1.9)	15 (2.2)	0 (0.0)	0.24
Cryoglobulinemic glomerulonephritis	6 (0.8)	5 (0.7)	1 (1.0)	0.58
Fibrillary glomerulonephritis	15 (1.9)	13 (1.9)	2 (1.9)	1.0
Focal segmental glomerulosclerosis	185 (23.7)	155 (23.0)	30 (28.6)	0.22
Global glomerulosclerosis NOS	**99 (12.7)**	**93 (13.8)**	**6 (5.7)**	**0.02**
IgA nephropathy	62 (7.9)	54 (8.0)	8 (7.6)	1.0
Lupus nephritis	26 (3.3)	23 (3.4)	3 (2.9)	1.0
Membranous nephropathy	37 (4.7)	29 (4.3)	8 (7.6)	0.15
Minimal change disease	15 (1.9)	12 (1.8)	3 (2.9)	0.44
Membranoproliferative glomerulonephritis	6 (0.8)	5 (0.7)	1 (1.0)	0.58
Oxalate nephropathy	**11 (1.4)**	**6 (0.9)**	**5 (4.8)**	**0.009**
Postinfectious glomerulonephritis	**36 (4.6)**	**24 (3.6)**	**12 (11.4)**	**0.001**
Thrombotic microangiopathy	16 (2.1)	15 (2.2)	1 (1.0)	0.71
Tubulointerstitial nephropathy and fibrosis	19 (2.4)	19 (2.8)	0 (0.0)	0.09

Note: n (%).
Abbreviations: DKD, diabetic kidney disease; non-DKD: nondiabetic kidney disease.
[a]Anti-GBM nephritis, arteriosclerosis, C3 glomerulonephritis, cast nephropathy, dense deposit disease, Fabry disease, genetic kidney disease, immunotactoid glomerulonephritis, light chain proximal tubulopathy, monoclonal immunoglobulin deposition diseases, and proliferative glomerulonephritis with monoclonal IgG deposits are not included in this table when the 'n' for 'All non-DKD' ≤5.

40% missing data, these variables were not included in the multivariate analysis. This finding highlights the necessity for future studies to ensure greater completeness in serology work-up with similarly large sample size, and clinically, patients with diabetes mellitus and proteinuria should have basic serological screening. Such studies should incorporate multivariate analysis to confirm whether these variables (C3, C4, p-ANCA/MPO, c-ANCA/PR3, and serology) are significantly associated with non-DKD. However, the practical challenge remains. In clinical settings, clinicians often refrain from extensive serology work up in patients predominantly suspected of having DKD, presenting a hurdle in gathering such data for future research. Our data underscore a prevailing clinical practice, namely, in cases in which patients exhibit proteinuria and diabetes, accompanied by multiple macro- and micro-level complications, advanced serologic tests are often not pursued in the interest of high-value care. These patients are typically treated without a kidney biopsy, because the pre-biopsy probability of DKD is deemed high. Consideration should be given to expanding serologic work-up in patients with diabetes and proteinuria to explore all potential etiologies before making a presumed diagnosis of DKD.

The limitations of our study include its retrospective nature, contributing to using only data that are available, and the absence of variables, such as duration of diabetes duration (especially in those with drug induced diabetes), lack of follow up data, macro- and micro-level complications predictor of DKD other than retinopathy[7,9-12,17] and lack of Tervaet's classification on biopsies.[19] Although this limitation arises from the retrospective nature of the study, resulting in incomplete data for some patients across these variables, these are factors that are already well established as predictors of DKD and would likely not provide new information for the purposes of this study. Nevertheless, our study's strength lies in its large sample size and statistical power. It represents, to the best of our knowledge, the largest study of native kidney biopsy-proven cases aiming to investigate the clinical factors associated with non-DKD versus DKD. Additionally, this cohort included patients with diabetes who did have biopsy, so this is likely a cohort in which clinical factors prompted kidney biopsy potentially leading to selection bias in the amount of non-DKD detected. Hence, these results likely represent a ceiling (maximum) for alternative causes of kidney disease in people with diabetes. Nevertheless, it provides useful information regarding the factors associated with finding non-DKD in this population of patients.

In conclusion, among patients with diabetes who underwent kidney biopsy, only 37.2% had DKD alone, and a very large amount (62.8%) had findings in addition to DKD on biopsy. Our study has identified several clinical parameters associated with finding non-DKD in the setting of diabetes, such as lack of retinopathy, lower hemoglobin A1c levels, preserved eGFR, microalbuminuria (vs macroalbuminuria), and lower degree of random UPCR. This

provides valuable information for clinicians on when kidney biopsy should be considered among patients with diabetes to capture all etiologies of proteinuria and kidney dysfunction.

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