Histopathologic and Clinical Features in Patients with Diabetes and Kidney Disease

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Abstract

Background The discovery of nondiabetic kidney disease (NDKD) in an individual patient with diabetes may have significant treatment implications. Extensive histopathologic data in this population are lacking, but they may provide insights into the complex pathogenesis of diabetic nephropathy (DN) and reveal specific phenotypes for the development of targeted therapies. This study seeks to elucidate the clinical and laboratory parameters associated with the spectrum of kidney histopathologic features in patients with diabetes.

Methods This study is a retrospective analysis of 399 kidney biopsies assessed from 2014 to 2016 at the University of Washington among patients with diabetes. More comprehensive clinical data were evaluated in a subset of 79 participants.

Results Of the 399 biopsies reviewed, 192 (48%) had a primary diagnosis of DN (including 26 with an additional diagnosis), and 207 (52%) had a primary diagnosis of NDKD (including 67 who also had DN). Retinopathy (sensitivity: 0.86; specificity: 0.81; OR, 27.1; 95% CI, 6.8 to 107.7) and higher levels of proteinuria (7.6 versus 4.1 g/d; $P=0.004$) were associated with DN, whereas a physician description of AKI was associated with a lower risk of DN (OR, 0.13; 95% CI, 0.04 to 0.38). The four most prevalent diagnoses in participants with NDKD were FSGS in 39, nephrosclerosis in 29, IgA nephropathy in 27, and acute tubular injury in 21.

Conclusions Among patients with diabetes who undergo kidney biopsy in the Pacific Northwest, approximately half have DN, and half have NDKD. Retinopathy and more severe proteinuria were associated with DN, and AKI was a more common descriptor in NDKD.

Introduction

CKD affects about one-quarter of people with diabetes in the United States (1), many of whom receive a diagnosis of diabetic kidney disease on clinical grounds. However, from an epidemiologic perspective, the risk of a reduced eGFR attributable to diabetes is about 50% (2). Determining which clinical signs are "atypical" for diabetic nephropathy (DN), defined as typical histopathologic findings on kidney biopsy, can be challenging. Proposed indications for kidney biopsy in this population include nephrotic-range proteinuria, hematuria, and a sudden decline in kidney function, but these have not been rigorously evaluated. A recent meta-analysis of 48 studies of kidney biopsies in patients with diabetes revealed significant heterogeneity in the prevalence of nondiabetic kidney disease (NDKD), ranging from 3% to 83% (3). Further, previous studies have not attempted to diagnose the primary disease process in patients with features of both DN and NDKD, although this information is

paramount to clinical decision making. Because DN is a heterogenous disease, histopathologic patterns may identify specific phenotypes for future clinical studies, as is the case for histologic variants of FSGS (4). We, therefore, sought to characterize the clinical signs, primary diagnosis, and histopathologic characteristics of a large cohort of patients with diabetes who underwent kidney biopsy in the Pacific Northwest.

Materials and Methods

Patient Population

We obtained institutional review board approval for access to patient records. We included adults with diabetes who underwent a native kidney biopsy read at the University of Washington (UW), a regional referral center for the Pacific Northwest, from 2014 to 2016. We identified potential participants using International Classification of Diseases (ICD) 9/ICD10

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codes for diabetes and a search of kidney biopsy pathology reports using natural language processing (searching for the terms "diabetes" and "diabetic"). We initially identified 4258 potentially qualifying patients biopsied from 2005 to 2016, of which 1315 were excluded for concurrent ICD9/ICD10 codes for kidney transplant. To reflect the most contemporary biopsy practices, patients were then restricted to those biopsied during the time period between June 2014 and June 2016. The resulting 531 biopsy reports were manually reviewed, leading to the exclusion of 100 patients who did not actually have diabetes and 32 patients who had a biopsy of a kidney mass, a kidney transplant, or insufficient quality for diagnosis. The final dataset comprised 399 participants for analysis (Figure 1).

Data Acquisition

Clinical information, pathologic diagnosis, and histologic findings were manually extracted from pathology reports and entered into a customized RedCap database. Laboratory data and demographic information were acquired through data extraction from electronic medical records using ICD9/ICD10 codes. The algorithm was designed to provide the data closest in time to when the biopsy was performed. Of the 399 participants, 79 were seen by a nephrologist within the UW health care system. In this UW subset, we were able to verify pathology report data and acquire additional clinical and laboratory information, including the presence or absence of a chart history of retinopathy and hypertension, diabetes type (1 or 2), duration of diabetes, and the use of inhibitors of the renin-angiotensin-aldosterone system or immunosuppression. Abnormal serology was defined as a clinical history of positive antinuclear antibody, ANCA, antiglomerular basement membrane (anti-GBM) antibody, or low complement levels. Proteinuria was reported on spot specimens as grams of protein per gram of creatinine. We considered spot urine specimens to be equivalent to a 24-hour urine collection. The presence or absence of AKI was ascertained by chart review of nephrology notes.

Classification Scheme

Biopsies were categorized into two groups, DN and NDKD, with cases that included findings of both classified by the primary diagnosis for analysis. We chose this approach because the primary diagnosis is the most likely to direct treatment decisions and is, therefore, the most clinically relevant. The criteria for a diagnosis of DN required the following three pathologic findings: (1) GBM thickening, (2) mesangial expansion, and (3) arteriolar hyalinosis (5). We also classified several histologic findings as concomitant findings to DN rather than a separate diagnosis: (1) acute tubular injury if noted secondary to DN, (2) arteriosclerosis,
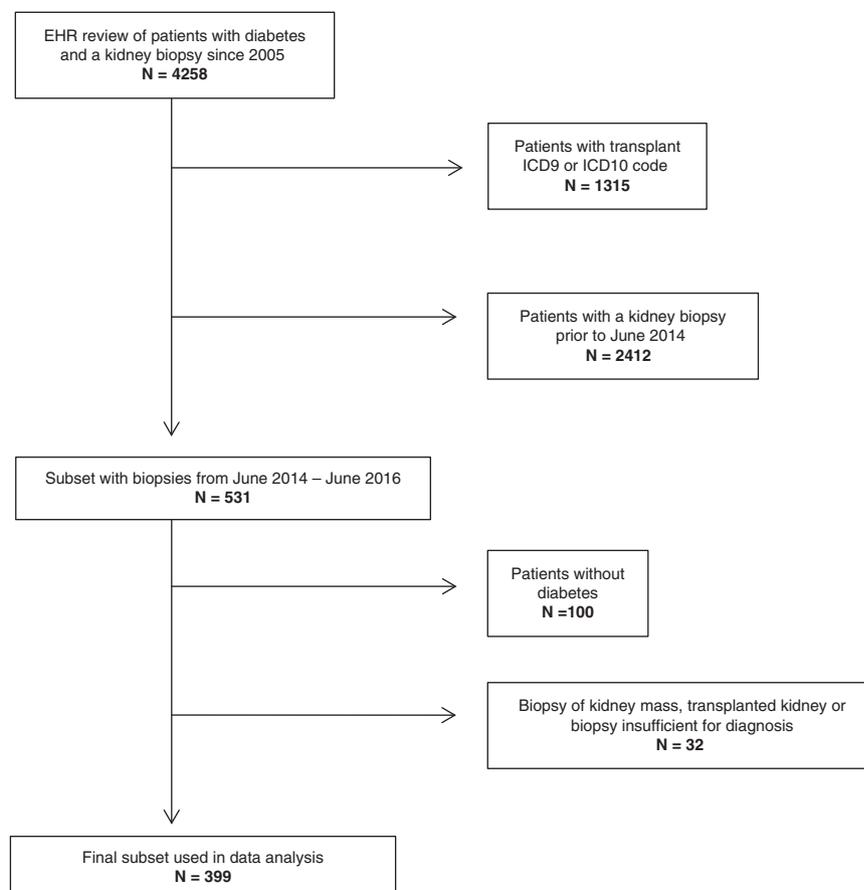

Figure 1. | **Consort diagram.** ICD, International Classication of Diseases.

(3) patchy eosinophilic infiltrate if noted secondary to DN, (4) global glomerulosclerosis, (5) FSGS if not primary, (6) tubular atrophy, (7) interstitial fibrosis, (8) interstitial inflammation, (9) Kimmelstiel–Wilson nodules, (10) microaneurysms, (11) mesangiolysis, and (12) podocyte foot process effacement if not a primary podocytopathy (5). Two reviewers independently reviewed the pathologic diagnoses to ensure proper classification, and any discordance was resolved through discussion with a renal pathologist. FSGS was classified as the primary diagnosis (NDKD) if the biopsy showed extensive foot process effacement but no evidence of advanced DN. It was classified as likely secondary to DN for any case with advanced DN or at least moderate DN with subnephrotic-range proteinuria and segmental foot process effacement (6). All of the cases of FSGS were reviewed by a renal pathologist.

Statistical Analyses

Distributions of each biopsy characteristic were summarized using descriptive statistics, such as the mean and SD for continuous variables or number and percent of non-missing responses for categorical variables. For continuous variables, we compared means of those with DN and those with NDKD *via* a two-sample t test assuming unequal variances; for categorical variables, we compared the distributions between these two groups using a chi-squared test. To evaluate the association of key clinical covariates and biopsy findings in the UW subset, we used logistic regression to estimate odds ratios (ORs) and associated 95% confidence intervals (95% CIs) and P values; we also calculated the sensitivity, specificity, positive predictive value, and negative predictive value of the clinical covariate for DN. All analyses were performed with R version 3.6.2 computing environment (R Foundation for Statistical Computing).

Results
Patient Characteristics

The study cohort included 399 participants: 230 men and 169 women. The mean age of our participants was 58 years, and 55% were White. Average serum creatinine was 3 mg/dl (SD 2.4 mg/dl), and eGFR was 36 ± 28 ml/min per 1.73 m². Proteinuria was quantified at 6.2 (SD 5) g/d, with nephrotic-range proteinuria occurring in about half of participants. Average hemoglobin A1c was 7.9%. Our subset of 79 participants with more comprehensive clinical information available (UW subset) was similar to the overall cohort (Table 1). Data on retinopathy were available on 61 of the 79 participants, and only seven participants had a diagnosis of type 1 diabetes. Sixty-eight percent of participants in the subset were prescribed medications that inhibited that the renin-angiotensin-aldosterone axis (Supplemental Table 1).

Table 1. Characteristics assessed by pathology report of 399 participants with diabetes who underwent kidney biopsy in the Pacific Northwest, including a subset of 79 with more extensive clinical data charted

Sample Population	Cohort of $N=399$ Patients		Subset of $N=79$ Patients	
	No. with Data	Mean (SD) or N (%)[a]	No. with Data	Mean (SD) or N (%)[a]
Demographics				
Age, yr, mean (SD)	398	57.6 (13.1)	78	53.6 (12.4)
Men	398	230 (58)	78	53 (68)
Race/ethnicity				
White	130	71 (55)	70	38 (54)
Black	130	18 (14)	70	10 (14)
Asian	130	23 (18)	70	10 (14)
Native American/Pacific Islander	130	8 (6)	70	5 (7)
Hispanic	130	10 (8)	70	7 (10)
Medical history				
AKI	399	98 (25)	79	26 (33)
Rapid decline in eGFR	399	91 (23)	79	23 (29)
SLE	399	7 (2)	79	4 (5)
Organ transplant	399	12 (3)	79	6 (8)
Diagnostic results				
Proteinuria	399	312 (78)	79	59 (75)
Nephrotic range	399	196 (49)	79	41 (52)
Hematuria	399	80 (20)	79	20 (25)
Abnormal serology	399	78 (20)	79	18 (23)
Monoclonal gammopathy	399	33 (8)	79	11 (14)
HCV antibody	399	33 (8)	79	16 (20)
Laboratory values				
Serum creatinine, mg/dl	302	3.0 (2.5)	77	2.9 (2.1)
eGFR, ml/min per 1.73 m²	301	35.7 (28.2)	76	38.7 (29.3)
Proteinuria, g/d[a]	223	6.2 (5.1)	67	5.7 (5.0)
HbA1c, %	72	7.9 (2.5)	59	7.8 (2.2)
Biopsy characteristics				
Biopsy size (LM)	395	1.3 (0.4)	79	1.2 (0.4)
No. of glomeruli	399	18.7 (10.4)	79	20.2 (11.0)

HCV, Hepatitis C virus; HbA1c, hemoglobin A1c; LM, light microscopy.
[a]Proteinuria from spot specimens was assumed to be equivalent to grams per day.

Table 2. Total cohort characteristics by primary diagnosis of diabetic nephropathy or nondiabetic kidney disease (N=399)

Sample Population	Diabetic Nephropathy, Mean (SD) or N (%)[a]	Nondiabetic Kidney Disease, Mean (SD) or N (%)[a]	P Value
No.	192	207	
Demographics			
Age, yr, mean (SD)	55.8 (13.0)	59.3 (13.0)	0.007
Men	111 (58)	119 (58)	0.99
Race/ethnicity			
White	29 (50)	42 (58)	0.36
Black	7 (12)	11 (15)	
Asian	15 (26)	8 (11)	
Native American/Pacific Islander	3 (5)	5 (7)	
Hispanic	4 (7)	6 (8)	
Diagnostic results			
Proteinuria	158 (82)	154 (74)	0.07
Nephrotic range	116 (60)	80 (39)	<0.001
Hematuria	25 (13)	55 (27)	0.001
Abnormal serology	26 (14)	52 (25)	0.005
Monoclonal gammopathy	17 (8)	16 (8)	0.82
HCV antibody	16 (8)	17 (8)	0.99
Laboratory values			
Serum creatinine, mg/dl	2.8 (2.4)	3.2 (2.5)	0.20
eGFR, ml/min per 1.73 m^2	36.2 (26.3)	35.3 (29.8)	0.79
Proteinuria, g/d[a]	7.5 (5.1)	4.9 (4.8)	<0.001
HbA1c, %	8.3 (2.7)	7.6 (2.2)	0.22

P values are from the t test assuming unequal variances or the chi-squared test, as appropriate. HCV, Hepatitis C virus; HbA1c, hemoglobin A1c.
[a]Proteinuria from spot specimens was assumed to be equivalent to grams per day.

Characteristics by Diagnosis

In the entire study cohort, 192 (48%) had a primary diagnosis of DN, and 207 (52%) had a primary diagnosis of NDKD. Of participants with a primary diagnosis of DN, 26 had a second diagnosis of NDKD. Sixty-seven participants with NDKD had a second diagnosis of DN. Overall, 93 (23%) of the total cohort had evidence of both NDKD and DN. Nephrotic-range proteinuria was significantly more prevalent in participants with DN (60%) than NDKD (39%). Mean proteinuria was also higher at 7.5 g/d in DN versus 4.9 g/d in NDKD. Abnormal serologies (ANCA, antinuclear antibody, and low complement) and hematuria

Table 3. Crosstabulations: Association of key clinical predictors assessed by chart review and biopsy findings in the subcohort (N=79)

Variable	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Odds Ratio (95% Confidence Interval)	P Value
Retinopathy	0.86	0.81	0.81	0.87	27.1 (6.82 to 107.77)	<0.001
AKI	0.17	0.39	0.18	0.37	0.1 (0.04 to 0.38)	<0.001
Rapid decline of eGFR	0.34	0.98	0.92	0.65	22.4 (2.75 to 183.09)	0.004
Type 1 DM	0.09	0.91	0.43	0.56	0.9 (0.20 to 4.48)	0.94
Type 2 DM	0.83	0.20	0.45	0.60	1.3 (0.39 to 3.90)	0.71
Duration of DM <10 yr	0.41	0.46	0.44	0.43	0.6 (0.21 to 1.75)	0.36
eGFR<30 ml/min per 1.73 m^2	0.68	0.25	0.50	0.42	0.7 (0.18 to 2.77)	0.63
eGFR (continuous), per 15-ml/min per 1.73 m^2 increment					1.0 (0.74 to 1.46)	0.84
Urine protein <3.5 g/g	0.14	0.76	0.43	0.42	0.5 (0.10 to 2.86)	0.47
Urine protein (continuous), per 1-g/g increment					1.1 (0.97 to 1.28)	0.14
Abnormal serology	0.23	0.59	0.31	0.49	0.4 (0.16 to 1.15)	0.09
Hematuria (any)	0.45	0.36	0.32	0.50	0.5 (0.16 to 1.43)	0.19
HbA1c<8.0%	0.57	0.35	0.44	0.48	0.7 (0.26 to 2.10)	0.56
HbA1c (continuous), per 1.0% increment					1.0 (0.81 to 1.29)	0.83

Crosstabulation analysis of the subgroup of 79 patients looking at sensitivity, specificity, positive predictive value, negative predictive value, odds ratio, and P values for diabetic nephropathy. DM, diabetes mellitus; HbA1c, hemoglobin A1c.

were observed statistically significantly more often in participants with NDKD. The presence of a monoclonal gammopathy was not statistically different between groups (Table 2).

Our UW subset of 79 participants provided more detailed clinical information verified by chart review. The sensitivity and specificity of a chart history of retinopathy for primary DN were 0.86 and 0.81, respectively, with an OR for DN of 27.1 (95% CI, 6.82 to 107.77). "AKI" was referenced less frequently (OR, 0.1; 95% CI, 0.04 to 0.38) in participants with DN. Nephrotic-range proteinuria was common in both groups, and proteinuria <3.5 g/d was not significantly associated with DN (OR, 0.5; 95% CI, 0.10 to 2.86). The presence of hematuria did not aid in differentiation of NDKD from DN (OR, 0.5; 95% CI, 0.16 to 1.43) when its presence or absence was confirmed by chart review (Table 3).

Histopathologic Findings

Among the study cohort, 192 participants had a primary diagnosis of DN. Glomerular involvement, such as global glomerulosclerosis, FSGS, and podocyte foot process effacement, was a concomitant finding to DN in 97%, 61%, and 84% of participants, respectively. The classic finding of Kimmelstiel–Wilson lesions was noted in 68%. Other histologic features included acute tubular injury in 23% and eosinophilic infiltrate in 17% (Figure 2). FSGS and acute tubular injury (as nonprimary diagnoses) were more likely to be found in participants with DN than those with a primary diagnosis of NDKD.

Twenty-four different diagnoses were identified in the 207 participants with primary NDKD. The four leading diagnoses were FSGS in 39, nephrosclerosis in 29, IgA nephropathy in 27, and acute tubular injury in 21 (Figure 3). Thirty-nine percent of this group had diagnoses with treatment options beyond standard care for diabetic kidney disease. These comprised membranoproliferative GN, membranous nephropathy, crescentic GN, amyloidosis, cast nephropathy, monoclonal Ig deposition disease, fibrillary GN, minimal change disease, C3 GN, acute interstitial nephritis, collapsing FSGS, and lupus nephritis (Supplemental Table 2). The proportions of participants with nephrosclerosis and FSGS were similar among all races/ethnicities (Supplemental Table 3).

Discussion

In our cohort of 399 participants with diabetes selected for kidney biopsy in the Pacific Northwest, we found that 48% had a primary diagnosis of DN and that 52% had a primary diagnosis of NDKD. Twenty-three percent had evidence of both DN and NDKD. Retinopathy and higher mean proteinuria were associated with a primary diagnosis of DN, whereas a clinical history of AKI was associated with NDKD. Participants with DN as the primary diagnosis frequently had findings of global glomerulosclerosis and FSGS. The leading diagnoses among participants with NDKD were FSGS, nephrosclerosis, IgA nephropathy, and acute tubular injury. Our classification scheme enabled us to determine that 20% of the total cohort carried diagnoses that favored treatment beyond standard therapies for diabetic kidney disease.

Although an association between retinopathy and DN is well known, the strength of this association in our study was nonetheless surprising. Retinopathy was 86% sensitive and 81% specific for DN, with an OR of 27 (95% CI, 6.82 to 107.77). Our magnitude of association was larger than that in a meta-analysis of 26 studies, which found an OR of 5.67 (95% CI, 3.45 to 9.34) (7), but it was similar to the largest contemporary single-center study, which restricted inclusion to patients with a dilated optic fundus examination. In that study, difficult cases were confirmed with eye-ground photography or fundus fluorescence angiography, suggesting that the greater strength of association may lie in more precise ascertainment of the diagnosis of retinopathy (8).

Our finding that more severe proteinuria is more likely to be found in DN rather than NDKD confirms the other two United States studies that evaluated proteinuria (9,10). This observation may be due to the high rate of FSGS in our cohort with DN. Because we did not assess changes in proteinuria over time, these results do not inform decisions in patients with a sudden increase in proteinuria. On the basis of these collective data, progressive severe proteinuria should not be the sole indication to biopsy patients with diabetes, such as has been recommended in the past.
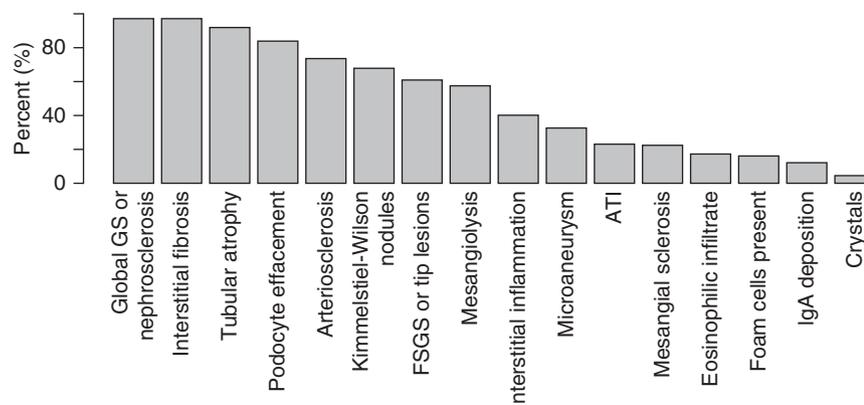

Figure 2. | Histologic findings in patients with a primary diagnosis of diabetic nephropathy. ATI, acute tubular injury; GS, glomerulosclerosis.
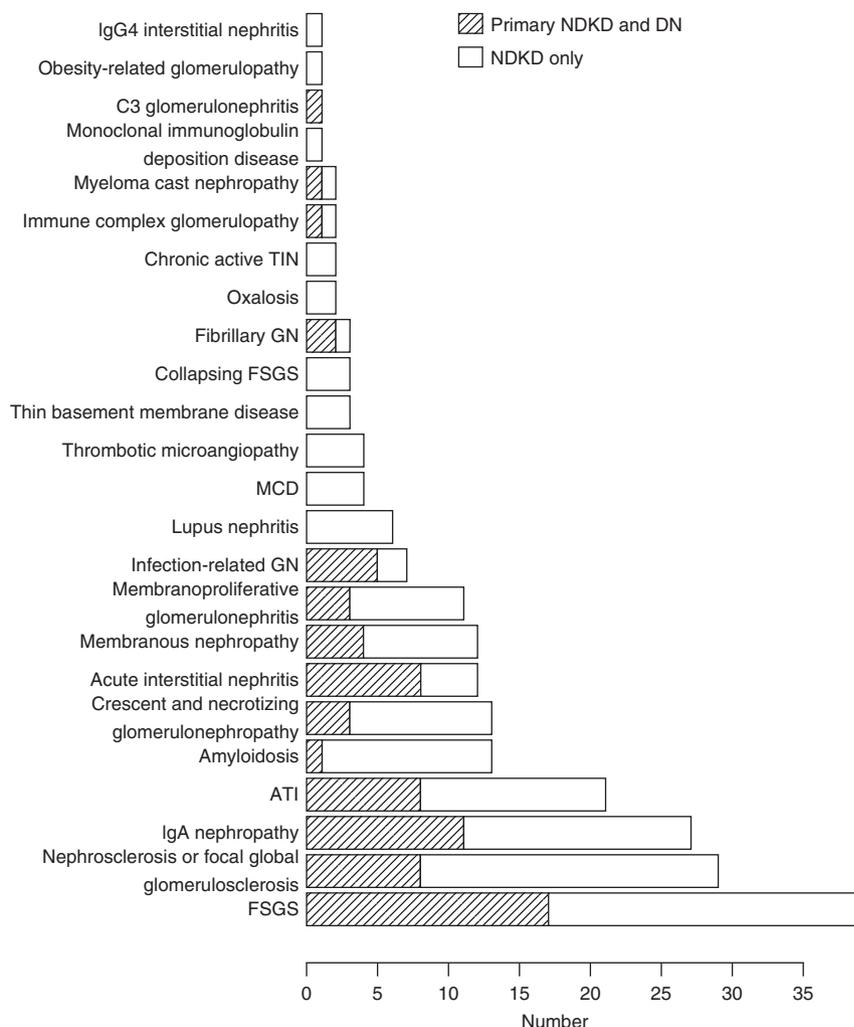
Figure 3. | The distribution of diagnoses in participants with a primary diagnosis of nondiabetic kidney disease. Thirteen biopsies had both FSGS and nephrosclerosis and were included in both categories. DN, diabetic nephropathy; MCD, minimal change disease; NDKD, non-diabetic kidney disease; TIN, tubulointerstitial nephritis.

The term "AKI" in the clinical history was associated with NDKD, whereas "rapid decline in eGFR" was associated with DN. Working groups have defined AKI as a rise in creatinine occurring over 7 days or less and a "rapid decline in eGFR" as a drop in eGFR>5 ml/min per year (11,12). The eGFR decline in persons with diabetes and advanced kidney disease with nephrotic-range proteinuria similar to our population may be about 1 ml/min per month, indicating a rapid decline but not an AKI (13). In contrast, of the numerous diagnoses in our NDKD category, many may present clinically with AKI (9,14). In our study, we evaluated the use of these terms by the referring physician. Data that quantify changes in eGFR over time are required to confirm these findings.

Clinical characteristics that did not aid in differentiation between DN and NDKD included hematuria, monoclonal gammopathy, and duration of diabetes. Glomerular hematuria is considered atypical in diabetic kidney disease and has been a criterion for inclusion in studies of NDKD in patients with diabetes (15,16). However, multiple studies

have failed to show a correlation between hematuria and NDKD, except in cohorts with a high prevalence of IgA nephropathy (8,17–19). Hematuria was noted more frequently in the clinical history of the pathology report in the NDKD group. However, in our UW subset in which we verified the presence or absence of hematuria, this finding had poor sensitivity and specificity for DN. The reason for this difference may be that other factors suggesting a GN may influence the referring clinician's clinical history.

We included the presence of a monoclonal gammopathy as a clinical parameter as it is associated with a diverse group of kidney diseases that may cause proteinuria and a decline in eGFR (20). Its presence increases with age and is present in 3% of people over the age of 50 and 5% of people older than 70 (21). Sharma *et al.* (9) found that a monoclonal gammopathy was associated with NDKD, but only 24% of participants with a positive M spike had related pathologies, such as cast nephropathy or amyloidosis. In our population, a monoclonal gammopathy was noted on the pathology report in 8% of patients and did not aid in differentiation of

DN from NDKD. This test may offer greater discriminating power when paired with free light-chain ratios adjusted for eGFR rather than on its own (22). Studies that include negative serum protein electrophoresis results are needed to describe the specificity of this test. In our study, a duration of diabetes of <10 years was not associated with NDKD, which may be because most of our patients had a longer duration. Previous studies have shown that shorter duration of diabetes (<5 years) is associated with NDKD, whereas longer duration (>10 years) is associated with DN (8,9,15,23,24).

The histopathologic findings among patients with DN shed light upon the complex pathogenesis of this disease. GBM thickening occurs early in diabetes and can be detected in the absence of microalbuminuria (25). The disease subsequently progresses to mesangial expansion, Kimmelstiel–Wilson lesions, and global glomerulosclerosis (26). We therefore chose GBM thickening and mesangial expansion as two of three criteria in establishing the diagnosis of DN. Notably, 80% of these biopsies had moderate to severe GBM thickening, and >70% showed moderate to severe mesangial expansion, consistent with the long duration of disease in our cohort.

Mesangiolysis may be a stage in the development of capillary aneurysms and mesangial nodules (Kimmelstiel–Wilson nodules), but the exact mechanisms are still unknown. One hypothesis is that capillary loops rupture when they lose their anchoring sites to degenerating mesangial cells, forming capillary aneurysms. Attempts by the mesangial cells to repair this damage may result in reactive nodules (27,28). Kimmelstiel–Wilson nodules and mesangiolysis were seen in the majority of our biopsies with primary DN, and microaneurysms were present in one-third.

Global glomerulosclerosis and FSGS were dominant findings among participants with DN. Experimental studies show that when the glomerular filtration surface area exceeds podocyte foot process coverage, proteinuria and lesions of FSGS develop (29), and loss of nephron mass accelerates this process (30). Therefore, two mechanisms likely contribute to these lesions in patients with diabetes: glomerulomegaly in the early stages and loss of podocytes and nephron mass in later stages (31). The mean proteinuria in our cohort of 6 g/d may reflect the selection of patients with greater proteinuria for kidney biopsy. Our rates of podocyte effacement, FSGS, and global glomerulosclerosis may account for the high levels of proteinuria in our cohort with DN. Biopsies from patients with diabetes and lower levels of proteinuria would be required to test this hypothesis.

The classic inflammation in DN is composed of T lymphocytes and macrophages, but our group has previously shown that eosinophilic infiltrate is prevalent in DN. We confirm these findings in our study in which eosinophilic infiltrate was present in 19% of our participants with DN (32). Our finding that acute tubular injury is more likely to occur with DN than without corroborates previous findings (9) and lends evidence to the argument that tubular injury may be involved in the pathogenesis of DN (33).

In patients with a primary diagnosis of NDKD, FSGS, nephrosclerosis, and IgA nephropathy were the most common lesions. The high prevalence of FSGS in our cohort is similar to that in every previous United States cohort

evaluating NDKD in patients with diabetes (9,10,34). By definition, the cases of FSGS in this group were not secondary to DN, but we were unable to ascertain whether these lesions represent primary FSGS or secondary FSGS. Because both hypertension and obesity are common comorbidities in this population and shared risk factors for secondary FSGS, they may have contributed to this pattern of injury (35,36). Similarly, nephrosclerosis increases with age and mean BP and was the second most common finding in our cohort with NDKD. The prevalence of IgA nephropathy among our entire cohort was 8.7% compared with 5.7% in the other large United States study. This result may stem from our higher proportion of Asian participants at 18% compared with 2% (9).

Thirty-nine percent of participants with NDKD and 20% of the entire cohort had a diagnosis with treatment options that could potentially reverse or forestall the progression of kidney disease. This is clearly the most relevant outcome to patients and providers when considering a biopsy. Our cohort includes participants with presentations that raised clinical suspicion for NDKD, but we are unable to retrospectively determine the degree of clinical suspicion. Many of the diagnoses found, such as membranoproliferative GN and minimal change disease, are virtually indistinguishable from DN without invasive testing. Others, such as membranous nephropathy, lupus nephritis, and pauci-immune GN, may be supported by serologic testing. Nevertheless, these numbers can be used in conjunction with the clinical characteristics we identified to inform clinical decision making in pursuing a kidney biopsy in this population.

The strength of this study lies in its size, generalizability, and classification scheme. Because the UW pathology department receives a high volume of biopsies from a regional referral base, we were able to select a narrow time period for analysis reflecting contemporary biopsy practices and medication use. The total cohort and the UW subset were similar in clinical characteristics, lending external validity to this study where much of the detailed clinical information was derived from the subset. Our classification scheme, which adjudicated the primary diagnosis for biopsies with features of both NDKD and DN, enabled us to quantify the effect on clinical decision making. The most significant limitation of this retrospective study is sampling bias as only patients with suspected NDKD were biopsied. In unselected populations with diabetes, the prevalence of NDKD is low (37,38). Our results should, therefore, be interpreted within this context. Additionally, we did not have longitudinal eGFR data to assess whether clinical or histopathologic characteristics were associated with a more aggressive course.

Our study adds to the global body of literature of NDKD in patients with diabetes. With the growing burden of diabetes in the United States (39), clinicians will be increasingly faced with the challenge of selecting patients for whom a kidney biopsy will favorably alter outcomes. Combining our results with those of similar studies suggest that retinopathy and GFR trajectory can guide clinical decision making. Prospective studies in which highly specific testing for diabetic retinopathy is performed at the time of kidney biopsy may reveal the true degree of this association. Additionally, serial measurements of GFR before and after protocol biopsies may demonstrate which histopathologic

features portend a more aggressive course. The spectrum of biopsy findings in people with diabetes is as diverse as the population it represents. Large-scale biopsy studies in people with diabetes who are more representative of the overall population are required to determine if this diversity is the norm or a result of sampling bias.

Disclosures

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Author Contributions

C. Alpers, N. Andeen, I. de Boer, B. Najafian, and R. Pichler conceptualized the study; I. de Boer, B. Najafian, T. Roark, and S. Sanghavi were responsible for data curation; I. de Boer, T. Roark, and S. Sanghavi were responsible for investigation; N. Andeen, I. de Boer, and R. Pichler were responsible for methodology; L. Zelnick was responsible for formal analysis; E. Ayers was responsible for project administration and resources; S. Sanghavi wrote the original draft; and T. Roark, L. Zelnick, N. Andeen, R. Pichler, E. Ayers, C. Alpers, B. Najafian, and I. de Boer reviewed and edited the manuscript.

Supplemental Material

This article contains the following supplemental material online at http://kidney360.asnjournals.org/lookup/suppl/doi:10.34067/KID.0003962020/-/DCSupplemental.

Supplemental Table 1. University of Washington subset characteristics.

Supplemental Table 2. Diagnoses among participants with primary nondiabetic kidney disease.

Supplemental Table 3. Histopathologic features by race/ethnicity.

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