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Original Article

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Renal Biopsy in Patients with Diabetes: Indications, Results, and Clinical Predictors of Diabetic Kidney Disease

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Abstract

Objective: Diabetic kidney disease (DKD) is one of the most common etiologies of end-stage kidney disease. Kidney biopsies are performed less frequently in patients with diabetes; however, these patients can have glomerular diseases other than diabetic nephropathy. We investigated the prevalence, etiologies, and clinical predictors of non-diabetic kidney disease (NDKD) in patients with type 2 diabetes.
Materials and Methods: The biopsy findings and clinical and laboratory features of 54 patients with type 2 diabetes were analyzed retrospectively.
Results: We found NDKD in 38 (60.4%) patients. We demonstrated that the presence of diabetic retinopathy was associated with an increased risk of DKD (p=0.048). Serum creatinine levels, microscopic hematuria, and diabetes duration were not found to be associated with NDKD. Proteinuria was found to be significantly higher in patients with DKD (p=0.044). The most common diagnosis was focal segmental glomerulosclerosis (25.9%). The second and third most frequent diagnoses were membranous nephropathy (11.1%) and rapidly progressive glomerulonephritis (7.4%), respectively.
Conclusion: Patients with diabetes may have NDKD. According to the high rate of NDKD in our study, we suggest that kidney biopsies in patients with diabetes, especially in those with atypical findings, should be performed more frequently.
Keywords: Type 2 diabetes mellitus, diabetic kidney disease, renal biopsy

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INTRODUCTION

The incidence and prevalence of diabetes mellitus (DM) is increasing worldwide and in Turkey. According to the latest data, the prevalence of DM in Turkey is 16.5% (1).

Diabetic kidney disease (DKD) is a major complication of DM and the leading cause of end-stage kidney disease (ESKD) in adult patients (2). DKD develops in 30% of patients with type 1 DM and 40% with type 2 DM (3).

Non-diabetic kidney disease (NDKD) can occur in patients with DM. NDKD and DKD can present coincidentally in a minority of patients. The prevalence of NDKD in patients with DM according to renal biopsy results has been reported to be variable, which is between 23%-73% (4-9).

Kidney biopsies are performed less frequently in patients with DM than other patients with proteinuria. Diagnosis of DKD is commonly made by clinical findings. Renal biopsy is generally carried out in patients with atypical clinical and laboratory features. Absence of diabetic retinopathy (DRP), progressive decline in kidney function, presence of hematuria, and short duration of DM can be the most frequent indications for kidney biopsy among patients with type 2 DM. Therefore, indications for kidney biopsy in patients with diabetes are not clear and are mostly determined by the subjective decision of the attendant physician and policies of the institution (10).

Making a definitive diagnosis of kidney disease in patients with DM is important because the treatments of

DKD and NDKD are different. NDKD may be treated specifically, whereas the standard of care in DKD is blood glucose control, treatment of hypertension, blockade of the renin-angiotensin-aldosterone system, lipid lowering treatment, and lifestyle changes, including weight loss and diet modifications (11).

Because of the different treatment modalities, making a precise diagnosis is of great importance.

In this study, we investigated the prevalence and etiologies of NDKD in patients with type 2 DM. This study also aimed to determine the clinical and laboratory predictors of DKD and NDKD.

MATERIALS AND METHODS

Patients and Data Collection

The data of 59 patients with type 2 DM, who underwent a kidney biopsy, were analyzed retrospectively. The kidney biopsies were performed between 2012 and 2019 in the department of nephrology. Of these, three patients with inconclusive pathological findings and two with NDKD superimposed on DKD were excluded and 54 patients were included. Type 2 DM was diagnosed according to the American Diabetes Association criteria (12). Hypertension is defined as a systolic blood pressure of ≥140 mm Hg and/or a diastolic blood pressure of ≥90 mm Hg measured in office or clinic (13). In all patients, kidney biopsies were performed owing to atypical clinical features. The indications were patients with acute onset nephrotic-range proteinuria, proteinuria but without accompanying diabetic retinopathy, rapid deterioration of kidney function, proteinuria and deterioration of kidney functions, proteinuria and positive rheumatologic serology or immunofixation tests, and proteinuria and hematuria along with progressive loss of kidney function. The indication for biopsy was proteinuria without accompanying diabetic retinopathy in 23 (42.5%) patients and proteinuria and deterioration of kidney function in 11 (20.4%) patients. The indication was acute onset nephrotic-range proteinuria in 8 (14.8%); deterioration of kidney function in 8 (14.8%); proteinuria and positivity in rheumatologic serology or immunofixation tests in 2 (3.7%); and proteinuria, hematuria, and progressive loss of kidney function in two (3.7%) patients. The biopsy indications of the patients are shown in Table 1.

Table 1. Biopsy indications

Biopsy indications	Number of patients, n (%)
Proteinuria without diabetic retinopathy	23 (42.5)
Proteinuria and increasing serum creatinine	11 (20.4)
Acute onset nephrotic-range proteinuria	8 (14.8)
Increase in serum creatinine	8 (14.8)
Proteinuria and positive autoimmune serology or immunofixation test	2 (3.7)
Proteinuria, hematuria, and serum creatinine	2 (3.7)

Demographic and clinical features and laboratory results were collected from the patients' file and electronic hospital records. The demographic and clinical features included age, sex, presence of hypertension, duration of DM, presence of DRP, and macrovascular and microvascular complications of DM. Microscopic hematuria, 24-hour urine protein amount or spot urine protein to creatinine ratio, serum creatinine, serum albumin, C-reactive protein (CRP), urine and serum electrophoresis, and rheumatologic serology tests (anti-nuclear antibody [ANA], complement C3 and C4 levels, anti-double stranded DNA, and anti-neutrophil cytoplasmic antibodies [ANCA]) were recorded. Laboratory results were collected at the time of the kidney biopsy. Microscopic hematuria is defined as >3 erythrocytes per high-power field. Microscopic albuminuria is defined as albuminuria from 30 to 300 mg/day in spot or 24-hour urine collection. Nephrotic-range proteinuria is defined as proteinuria >3.5 g/day in spot or 24-hour urine samples.

The study was approved by the Ethics Committee of Bezmialem Vakıf University (Approval Date: December 3, 2019; Approval Number: 22/421). Informed consent was obtained from all the patients.

Renal Biopsy

Kidney biopsies were examined by an experienced pathologist. For the light microscopy evaluation, the biopsy specimens were stained with hematoxylin-eosin, periodic acid-Schiff, Masson's trichrome, and methenamine silver. Staining with antibodies against IgG, IgM, and IgA; complements C3 and C1q; fibrinogen;

Main Points

- Non-diabetic kidney disease (NDKD) can occur in patients with DM. The prevalence of NDKD in patients with DM according to renal biopsy results has been reported to be variable, which is 23%-73%.
- We investigated the prevalence, etiologies, and clinical predictors of non-diabetic kidney disease (NDKD) in patients with type 2 diabetes.
- The amount of proteinuria was significantly higher in patients with DKD than in those with NDKD (p=0.044). There were no statistically significant differences between patients with DKD and those with NDKD in terms of age, sex, duration of DM, presence of hypertension, microscopic hematuria, diabetic retinopathy, and serum creatinine and albumin levels.
- Univariate regression analysis revealed that only the presence of DRP among these parameters was associated with an increased risk of diabetic nephropathy (p=0.048).
- According to the study data, many patients with diabetes may have potentially curable glomerular diseases other than DKD, and we suggest that renal biopsy may be a viable option for the diagnosis of patients with diabetes and with proteinuria, especially with atypical signs.

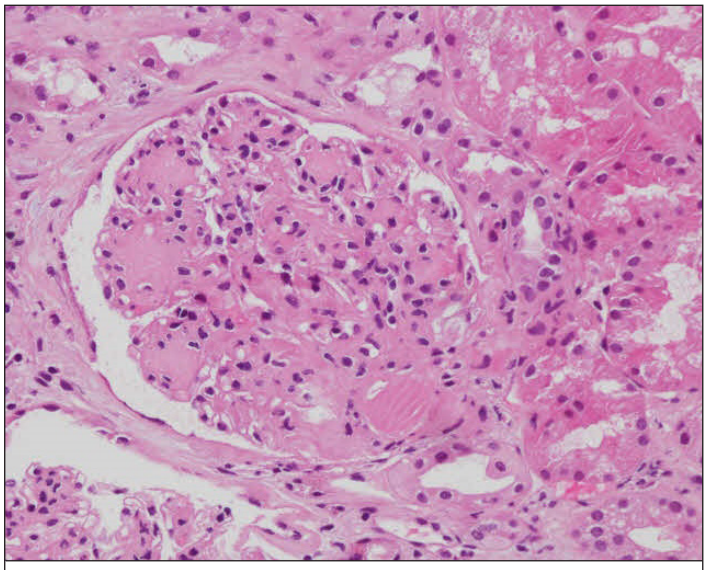

Figure 1. Mesangial cells are aligned around the nodular matrix. Kimmelstiel-Wilson lesion (haematoxylin & eosin, 200x)

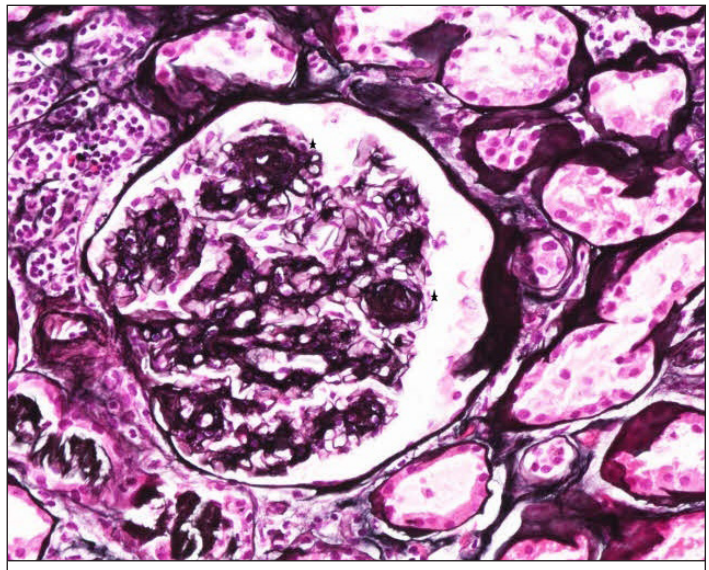

Figure 3. Diffuse and nodular (pointed by*) glomerular sclerosis (periodic acid-Schiff, 200x)

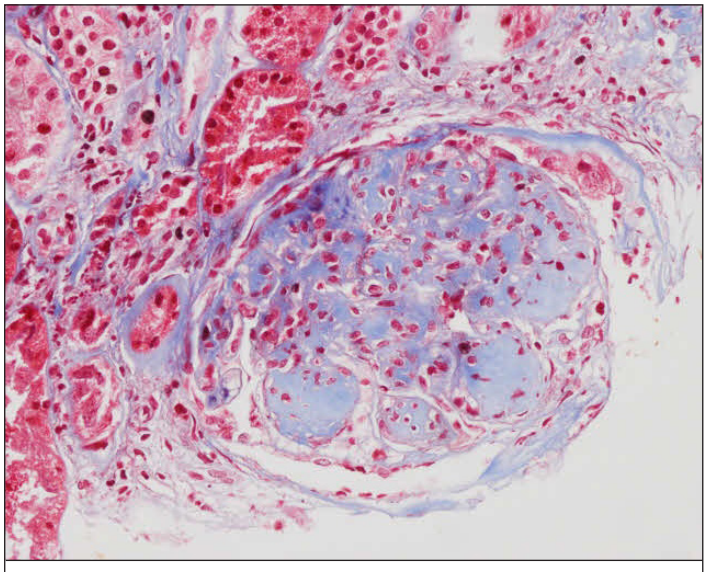

Figure 2. Glomerular nodular sclerosis (Masson's trichrome, 200x)

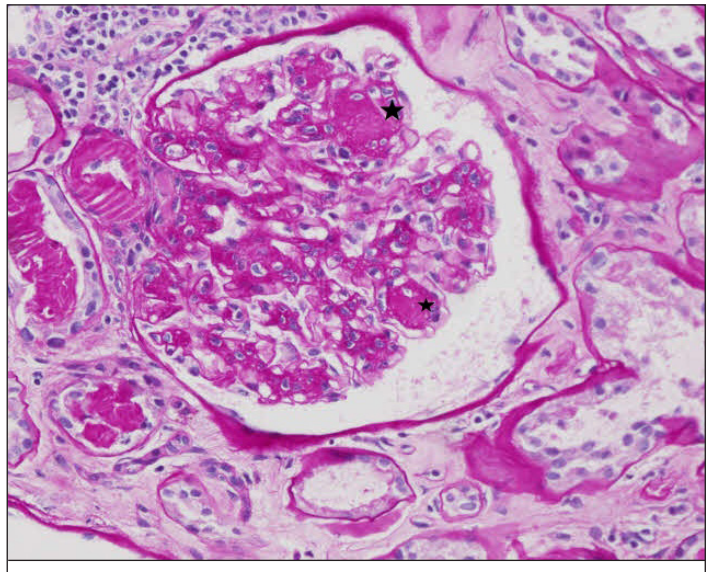

Figure 4. Glomerular sclerosis and arteriolar hyalinosis (periodic acid-Schiff, 200x)

and kappa and lambda light chains were carried out for immunofluorescence evaluation. Congo red stain was used when amyloidosis was suspected. The pathologic diagnosis of DKD was made by the following renal findings: glomerular basement membrane thickening, diffuse or nodular mesangial expansion, glomerulosclerosis, hyaline exudation in the glomeruli (fibrin cap), capsular drop or hyaline thrombi, and arteriolar hyalinosis (14).

According to the biopsy findings, the patients were distributed into 2 groups with the diagnosis of DKD and NDKD. NDKD is a general term that involves various glomerular and tubular diseases. Images of the DKD group are illustrated in Figures 1-5.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences version 20 (IBM Corp.; Armonk, NY, USA). Descriptive statistics were expressed as mean± standard deviation for continuous variables with normal distribution, median for continuous variables without normal distribution, and case numbers and percentages for categorical variables.

The significance of the difference between the groups was examined with the chi-squared and Fisher exact tests for categorical variables and the Mann-Whitney U and Student's t tests for continuous variables. Predictors of DKD were shown using logistic regression analysis. Presence of DRP and

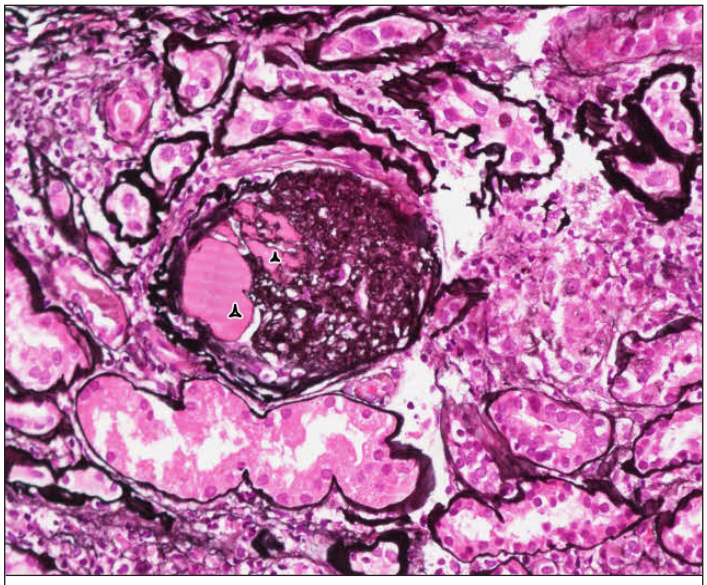

Figure 5. Microaneurysms in glomerulus (periodic acid-Schiff, 200x)

Table 2. Characteristics of patients

Patients characteristics	Results
Age (years)	59.80±10.53
Sex (women, %)	57.4
Diabetes duration (months)	120 (IQR: 50-195)
Microscopic hematuria (%)	26.4
Hypertension (%)	57.4
Diabetic retinopathy (%)	28.9
Serum creatinine (mg/dL)	1.43 (IQR: 0.9-2.8)
Proteinuria (g/day)	3,670 (IQR: 1,664.5-7,544.5)
Serum albumin (g/dL)	3.5±0.74
CRP (mg/L)	0.8 (IQR: 0.02-0.65)

IQR: interquartile range; CRP: C-reactive protein

amount of proteinuria were included as independent variables to the model, and p<0.05 was considered statistically significant.

RESULTS

A total of 54 patients were included in the study. 31 (57.4%) were women and 23 (42.6%) were men. Their mean age was 59.80±10.53 years. Median diabetes duration was 120 months (interquartile range [IQR]: 50-195). A total of 31 (57.4%) patients had a diagnosis of hypertension at the time of kidney biopsy. Of the 45 patients examined for DRP, 13 (28.9%) were diagnosed with DRP and 26 (57.8%) patients had no diabetic macrovascular and microvascular complications. Only DRP was present in 8 (17.8%) patients, 3 (6.7%) had DRP and coronary artery disease, 1 (2.2%) had DRP and diabetic polyneuropathy, 1 (2.2%) had a history of stroke and DRP, 4 (8.9%) had coronary artery disease, 1 (2.2%) had diabetic polyneuropathy, and 1 (2.2%) had a history of stroke.

Microscopic hematuria was detected in 14 patients (26.4%). Median serum creatinine values and proteinuria were 1.43 mg/dL (IQR, 0.9-2.8 mg/dL) and 3,670 mg/day (IQR 1,664.5-7,544.5 mg/day), respectively. Mean serum albumin value was 3.5±0.74 g/dL, and median value of CRP was found 0.8 mg/L (IQR 0.02-0.65 mg/L). The clinical and laboratory characteristics of the patients are shown in Table 2.

Urine immunofixation testing was performed in 16 patients; of them, eight had both kappa and lambda light chains, seven had no light chains, and one had kappa light chain. Serum immunofixation testing was performed in 18 patients; of them, 16 had no immunoglobulins, one had monoclonal kappa, and one had monoclonal lambda light chains.

No positive autoimmune serology was demonstrated in 41 (85.4%) patients, whereas four (8.3%) had positivity for ANA, three (4.2%) had positivity for perinuclear ANCA (p-ANCA), and one (2.1%) had positivity for both ANA and p-ANCA.

During pathologic examination, a mean of 21.48±10.63 glomeruli were examined. DKD was detected in 16 (29.6%) patients. Renal pathologies observed in patients with NDKD were focal segmental glomerulosclerosis (FSGS) in 14 (25.9%) patients, membranous nephropathy (MN) in six (11.1%) patients, rapidly progressive glomerulonephritis (RPGN) in four (7.4%) patients, acute interstitial nephritis (AIN) in three (5.6%) patients, crystal-induced nephropathy coincident with acute tubular damage in three (5.6%) patients, pure crystal nephropathy in two (3.7%) patients, multiple myeloma in two (3.7%) patients, crystal-induced nephropathy coincident with hypertensive nephrosclerosis in one (1.9%) patient, normal light microscopy findings in one patient (1.9%), IgA nephropathy in one (1.9%) patient, and post-infectious acute glomerulonephritis in one (1.9%) patient.

The amount of proteinuria was significantly higher in patients with DKD than in those with NDKD (p=0.044). However, there were no statistically significant differences between patients with DKD and those with NDKD in terms of age, sex, duration of DM, presence of hypertension, microscopic hematuria, diabetic retinopathy, and serum creatinine and albumin levels. Comparison of demographic, clinical, and laboratory parameters between the two groups are shown in Table 3.

In the DKD group, 11 of 16 patients had nephrotic-range proteinuria, whereas in the NDKD group, 17 of 38 patients had nephrotic-range proteinuria. There was no statistically significant difference between the two groups in terms of number of patients with nephrotic-range proteinuria.

Regression analysis was performed to evaluate the risk of different parameters in DKD and NDKD. These parameters were as-

Table 3. Comparisons between groups

	DKD (n=16)	NDKD (n=38)	p
Age (years)	61.19±7.76	59.21±11.55	0.53
Sex (women)	11	20	0.27
Diabetes duration (months)	120	120	0.50
Presence of hypertension	11	20	0.32
Presence of microscopic hematuria	3	11	0.51
Presence of diabetic retinopathy	7	6	0.09
Serum creatinine (mg/dL)	1.31	1.57	0.19
Serum albumin (g/L)	3.29±0.68	3.59±0.75	0.18
Amount of proteinuria (mg/day)	6,320	3,065	0.044*

*statistically significant
DKD: diabetic kidney disease; NDKD: non-diabetic kidney disease

Table 4. Regression analysis

	β	Standard error	OR	OR (95% CI)	p
Proteinuria	0.000	0.000	1	1-1	0.322
Presence of DRP	1.429	0.722	4.17	1.013-17.183	0.048*
Constant	-0.825				

*statistically significant
CI: confidence interval; OR: odds ratio; DRP: diabetic retinopathy

sumed to be possible predictors of DKD. The regression analysis model included age, sex, amount of proteinuria, diabetes duration, presence of diabetic complications and DRP, and serum creatinine value as variables. Univariate regression analysis revealed that only the presence of DRP among these parameters was associated with an increased risk of diabetic nephropathy (p=0.048; OR, 4.17; model accuracy, 72.7%). Other parameters were not found to be statistically significant (Table 4).

DISCUSSION

In this study, we retrospectively examined the results of kidney biopsy in 54 patients with type 2 DM. We found NDKD in 38 (60.4%) patients.

Indications for kidney biopsy in patients with diabetes are debatable, and it is mostly performed when atypical clinical and laboratory features are present, which are suggestive of NDKD. In our study, we defined new-onset nephrotic-range proteinuria, proteinuria without diabetic retinopathy, a rapid deterioration of kidney functions, proteinuria with accompanying deterioration of kidney functions, proteinuria with positive rheumatologic serology or immunofixation tests, proteinuria with hematuria, and a progressive loss in kidney functions as atypical clinical signs for DKD. We demonstrated that the presence of DRP was associated with an increased risk for DKD.

NDKD has been reported at different rates, and many clinical and laboratory signs are found to predict NDKD. In a study by Heybeli et al. (15), kidney biopsies of 115 patients were retrospectively examined; 40% of the patients had NDKD, 31.3% had DKD, and 28.7% had DKD and NDKD in combination. The absence of DRP and abnormal disease chronology were found to be independently associated with NDKD. Erdogmus et al. (16) have demonstrated that 50% of patients had NDKD. The presence of DRP was found to predict DKD. A study by Imtiaz et al. (17) has found the prevalence of NDKD to be 42.2%. A short duration of DM and absence of DRP were associated with NDKD. In our study, only 2 patients were diagnosed with DKD and NDKD in combination. These two patients were excluded from the study because we believed that analysis with such a low number of patients would give misleading results.

In our study, serum creatinine level, microscopic hematuria, and diabetes duration were not found to be associated with NDKD. Studies that investigated these laboratory and clinical values as surrogate markers to differentiate between NDKD and DKD have revealed conflicting results. According to a study by Akimoto et al. (18), microscopic hematuria may be a common characteristic in patients with DKD and with nephrotic-range proteinuria. In this study, 50 patients with type 2 DM were biopsied with a suspected diagnosis of NDKD. Of these, 34 patients had isolated diabetic nephropathy. Microscopic hematuria was found in a significantly higher percentage of patients with NDKD; however, when patients with nephrotic-range proteinuria were compared in terms of hematuria, no significant difference was found between the patients with DKD or NDKD. The investigators have also searched for the differences in the clinical characteristics between patients with hematuric and non-hematuric DKD; it has been found that patients with hematuria had a longer duration of DM and higher values of serum creatinine and proteinuria. They also had a higher incidence of DRP. In the pathologic examination, the prevalence of nodular lesions was higher but it was not statistically significant. It is suggested that hematuria may be a predictor of late-stage glomerular damage because of diabetes. Tone et al. (19) have shown in their study with 97 patients that microscopic hematuria had a low sensitivity and specificity for NDKD, whereas short duration of diabetes (<5 years) and absence of DRP had high sensitivity and specificity for NDKD. In contrast with these studies, a study of Chong et al. (20) has shown that the presence of AKI and microscopic hematuria predicted NDKD. The study included 110 patients with type 2 DM, and it was shown that a shorter duration of diabetes and lower serum creatinine levels may be a sign of NDKD. According to the study, a diabetes duration of >10 years and the presence of DRP predicted DKD. According to a study of Wu et al. (21), patients with DKD and microscopic hematuria had severe interstitial inflammation and hematuria associated with a higher risk of progression to ESKD.

In our study, proteinuria was found to be significantly higher in patients with DKD. In clinical practice, massive proteinuria is an issue of concern, suggesting accelerated loss of kidney function. This finding may cause most of the physicians to perform a kidney biopsy in patients with diabetes not to overlook a diagnosis other than DKD. Yang et al. (22) have retrospectively analyzed 213 patients with diabetes who underwent a kidney biopsy. Multivariate regression analysis showed that the absence of DRP, non-nephrotic-range proteinuria, and a glomerular filtration rate >90 mL/min significantly indicated NDKD. On the basis of the predictors shown in the logistic regression analysis, the authors developed a differential diagnostic model for predicting the development of NDKD. New patients, in whom a kidney biopsy was carried out, were evaluated with the model. It was shown that the model had a sensitivity of 94.4% and specificity of 83.8%. In our study, it was found that proteinuria in the non-nephrotic range was an indicator for NDKD. In another study, the authors have reported that nephrotic-range proteinuria predicts DKD (23). Nephrotic-range proteinuria is a sign of advanced DKD. Isolated non-nephrotic-range proteinuria in patients with diabetes is not a compelling indication for biopsy. In patients with DM and NDKD, kidney biopsy was mostly performed owing to the presence of atypical signs, which were earlier than other patients with diabetes and with proteinuria. This may be the reason for the higher levels of proteinuria in patients with DKD.

In a meta-analysis involving 48 studies with 4,876 participants, the prevalence of NDKD ranged from 3% to 82.9%. The most commonly seen NDKD diagnoses were IgA nephropathy in 16 studies, MN in 9 studies, FSGS in 6 studies, and AIN in 4 studies. Differential diagnoses of NDKD showed ethnic and geographical diversities. IgA nephropathy was most commonly seen in studies from Asia, whereas FSGS was the most frequent NDKD in studies from Europe and the United States of America (24). Heybeli et al. (15) and Erdogmus et al. (16) have demonstrated that FSGS and MN were the most common NDKD, respectively.

Compatible with the abovementioned meta-analysis and the study of Heybeli et al. (15), the most common diagnosis in our study was FSGS (25.9%). The second most frequent diagnosis was MN (11.1%). In our study, RPGN (7.4%) was found to be the third most frequent NDKD. The reason for the high percentage of RPGN diagnoses may be that a considerable number of patients (21 patients, 38.9%) had elevated serum creatinine levels.

The real prevalence of NDKD among patients with diabetes is very difficult to find because patients with diabetes with non-nephrotic-range proteinuria alone are usually not biopsied, and clinicians look for atypical clinical findings to perform a biopsy. This may be an explanation for the reports of generally high rates of NDKD among patients with diabetes. In two prospective randomized studies, DKD rates were reported. Cordonnier et al. (25) have investigated the effects of angiotensin-converting enzyme inhibition on renal structure and function in patients with diabetes. In this study, all the patients underwent baseline renal biopsy and those with NDKD were excluded. The patients had type 2 diabetes with a disease duration of more than two years with proteinuria levels between 70-4,210 mg/day and creatinine clearance more than 60 mL/min. Among 26 patients, 4 (15%) had NDKD. In a study of Schwartz et al. (26), the study participants had type 2 diabetes with a 24-hour urine protein excretion of more than 500 mg/day and a serum creatinine level less than 3 mg/dL. NDKD was found in 6% of the patients.

The retrospective nature of our study and low number of the participants are the two main limitations. Our study is compatible with other studies demonstrating that NDKD is commonly found in patients with diabetes and massive proteinuria, and DRP is a predictor of DKD.

Most of these studies are retrospective, and the patient numbers are limited. Their results give the clinicians only a presumption rather than a clear definition of which patient may have NDKD. According to the study data, many patients with diabetes may have potentially curable glomerular diseases other than DKD, and we suggest that renal biopsy may be a viable option for the diagnosis of patients with diabetes and with proteinuria, especially with atypical signs.

CONCLUSION

Patients with diabetes may have NDKD. Atypical clinical findings may be suggestive of NDKD, but none of the findings are highly specific or sensitive. On the basis of high NDKD rates in patients with diabetes with atypical clinical findings, we suggest that kidney biopsies should be more commonly performed in patients with diabetes, and attention must be paid to the patients with atypical clinical findings.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Bezmialem Vakıf University (Approval Date: December 3, 2019; Approval Number: 22/421).

Informed Consent: Informed consent was obtained from the patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - A.S.A., M.G., G.Ç.; Design - Ö.C.E., R.K.; Supervision - M.G., R.K.; Resources - G.Ç., Ö.C.E.; Materials - G.Ç.; Data Collection and/or Processing - A.S.A., M.G.; Analysis and/or Interpretation - M.G., A.S.A.; Literature Search - Ö.C.E.; Writing - A.S.A, R.K.; Critical Reviews - Ö.C.E., R.K.

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Conflict of Interest: The authors have no conflict of interest to declare.

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