Original Paper

Non-Diabetic Kidney Disease in Type 2 Diabetic Patients: Prevalence, Clinical Predictors and Outcomes

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Key Words

Diabetic kidney disease • Diabetic retinopathy • Kidney biopsy • Non-diabetic kidney disease • Type 2 diabetes mellitus

Abstract

Background/Aims: Diabetic kidney disease (DKD) is one of the most frequent microvascular complications of diabetes and is the leading cause of end-stage kidney disease worldwide. In patients with diabetes, non-diabetic kidney disease (NDKD) can also occur. NDKD can be either alone or superimposed with the DKD. In this study, we aimed to investigate the utility of kidney biopsy in patients with type 2 diabetes mellitus (T2DM) and the predictability of diagnosing DKD versus NDKD from clinical and laboratory data. We also evaluated the prevalence and etiology of NDKD in patients with T2DM. **Methods:** We retrospectively reviewed type 2 diabetic patients who had kidney biopsy in the last 10 years for diagnosing possible NDKD in our center. In all patients kidney biopsies were performed because of atypical clinical features and biopsy samples were examined by light and immunofluorescence microscopy. Clinical parameters, laboratory workup and office blood pressures were recorded for each patient at the time of biopsy. **Results:** Eight patients were excluded due to missing data. A total of 48 patients (female/male: 26/22 and mean age: 59±8 years) were included in the study. According to the biopsy findings, 24 (50%) patients had NDKD alone, 20 (41.7%) had DKD alone and 4 (8.3%) had coexisting DKD and NDKD. The most common NDKD diagnoses were membranous nephropathy (29.2%), tubulointerstitial nephritis (20.8%) and IgA nephropathy (12.5%). There were no significant differences in three groups with respect to the duration of diabetes, proteinuria, hematuria and glycated hemoglobin A1c levels. Diabetic retinopathy (DR) was the most significant finding, which was associated with DKD. Positive and negative predictive values of DR for DKD were 88 and 81%, respectively. **Conclusion:** This study demonstrated a high prevalence of NDKD in patients with T2DM. The absence of DR strongly predicted NDKD. Clinical decision alone can lead to wrong diagnosis and delay in appropriate

therapy. Clinicians should consider the kidney biopsy more liberally when there is uncertainty on the exact etiology of the kidney disease. However, prospective multicenter studies are needed to clarify the prognosis and outcomes of patients with diabetics.

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Introduction

Diabetic kidney disease (DKD) is one of the most significant microvascular complications of diabetes and is the leading cause of end-stage kidney disease (ESKD) requiring renal replacement therapy in adults. However, in diabetic patients kidney diseases other than DKD can develop [1, 2]. The prevalence of non-diabetic kidney disease (NDKD) is reported at different rates in the biopsied diabetic cohorts [3-18]. NDKD can occur either alone or superimposed on DKD. It is important to diagnose NDKD in diabetics because the treatment and prognosis of these diseases are quite different. The diagnosis of DKD is usually based on clinical features, clinicians' and/or single-center experiences. Among diabetic patients, the indications of kidney biopsy are debatable, and it is not performed routinely. Therefore, the correct diagnosis of such patients would be crucial for disease specific therapy [2]. In this study, we aimed to investigate the prevalence, risk factors and etiology of NDKD in patients with type 2 diabetes mellitus (T2DM).

Materials and Methods

Patients and data collection

Data were retrospectively analyzed from 56 patients with T2DM who had undergone a kidney biopsy from 2006 to 2016 at the Department of Nephrology, Ankara University School of Medicine, Ankara, Turkey. Eight patients were excluded from the study due to missing data and 48 patients were included in the study. The diagnosis of T2DM was based on the criteria of the American Diabetes Association (ADA, 2015) [19]. The included patients were followed-up for one year. At the end of the one-year follow-up period, ESKD requiring renal replacement therapy was recorded. In all patients kidney biopsies were performed due to atypical clinical features, which were classified into six groups (i) patients with acute onset nephrotic level proteinuria ($>3.5\text{gr/day}$) and normal renal functions; (ii) patients with previously normal renal functions, but that experience a rapid progression of renal function loss; (iii) patients who develop renal failure and/or nephrotic level proteinuria without accompanying diabetic retinopathy (DR); (iv) patients who had diabetes for less than 5 years who had nephrotic level proteinuria or renal failure; (v) patients with unexplained active urine sedimentation findings. The demographical, clinical characteristics and laboratory results of all patients were obtained from the patient files and electronic hospital records at the time of kidney biopsy. Demographical and clinical characteristics were recorded as; age, sex, office systolic and diastolic blood pressure, duration of diabetes and presence of DR. Among laboratory results, serum creatinine, serum albumin, spot urine analysis (microscopic hematuria was defined as >3 red blood cells per high-power field on urine examination), glycated hemoglobin A1c (HbA1c) levels, estimated glomerular filtration rate (eGFR) [calculated using the chronic kidney disease epidemiology collaboration (CKD-EPI) creatinine equation], 24-hour urine protein amount or spot urine protein/creatinine ratio were recorded.

Kidney biopsy and pathological examination

All kidney biopsies were performed with the consent of each patient. Kidney biopsy specimens were evaluated by two experienced pathologists simultaneously using standards for kidney biopsy including hematoxylin and eosin, periodic acid-Schiff, Masson's trichrome, periodic acid methenamine silver and Gentian Violet stains for light microscopy, and IgG, IgM, IgA antibodies, complement products C3 and C1q, Kappa and Lambda light chains and Fibrinogen for immunofluorescence microscopy. Biopsies contained an average of 9 glomeruli per biopsy. Diagnosis of DKD was based on the renal findings including glomerular basement membrane (GBM) thickening, mesangial expansion, nodular glomerulosclerosis, hyaline insudation in glomeruli in the form of fibrin cap, capsular drop or hyaline thrombi, arteriolar hyalinosis and

arteriosclerosis [20]. Immunofluorescence studies helped in differentiating diabetic glomerular lesions from NDKD. Diffuse linear staining of GBM and tubular basement membranes for IgG due to nonimmunological trapping of proteins in thickened abnormal basement membranes, and nonspecific entrapment of IgM, C3 and light chains were compatible with DKD. NDKD and/or superimposed kidney disease comprising of membranous nephropathy (MN), Ig A nephropathy, focal segmental glomerulosclerosis (FSGS), and tubulointerstitial nephritis (TIN) were differentiated by the histopathologic evaluation. We also assessed the chronic damage in the renal parenchyma by scoring the interstitial fibrosis and tubular atrophy on a scale of mild (<25%), moderate (25- 50%) and severe (>50%). According to the kidney biopsy findings patients were divided into three groups. Group I pure NDKD, group II pure DKD, and group III NDKD superimposed on DKD. Demonstrative figures of the kidney biopsies of each patient group are illustrated in Fig. 1.

Statistical analysis

Statistical analysis was performed using SPSS version 16 (SPSS Inc., Chicago, USA). Descriptive statistics were shown as mean $\pm$ standard deviation for variables with normal distribution, median (min – max) for variables without a normal distribution, and case number and percentage (%) for nominal variables. Continuous variables were studied using a paired t- test when the distribution in time before and after treatment is normal. When there are more than two groups, the significance of the difference between groups was examined using an ANOVA variance analysis test, and the significance of the difference with respect to mean values was examined using a Kruskal-Wallis test. Nominal variables were evaluated using Pearson's chi-square or Fisher exact tests. Results were considered statistically significant for $P < 0.05$.

Fig. 1. Demonstrative kidney biopsy findings of each patient group. A. Group I pure non-diabetic kidney disease; a case of IgA nephropathy showing pure mesangial proliferation and diffuse mesangial IgA deposits by immunofluorescence microscopy (inlet). B. Group II pure diabetic kidney disease; in this case the glomeruli revealed diffuse nodular mesangial sclerosis described as Kimmelstiel –Wilson nodules highlighted with trichrome stain (inlet) compatible with diabetic kidney disease. C. Group III non-diabetic kidney disease superimposed on diabetic kidney disease; a case of membranous nephropathy with diffuse mesangial expansion. Finely granular IgG deposits were found on the thickened glomerular basement membrane by immunofluorescence microscopy (inlet), and the mesangial expansion was the evidence of underlying diabetic kidney disease.

Results

A total of 48 T2DM patients were included the study. Based on kidney biopsy findings, 24 (50%) patients had NDKD alone, 20 (41.7%) had DKD alone and 4 (8.3%) had DKD and NDKD at the same time. At the time of kidney biopsy, average age was determined as 59±8 years, and the number of female patients was 26 (54%). The characteristics of patients are given in Table 1. Renal pathologies observed in the NDKD patient group were; 7 (29.2%) patients MN, 5 (20.8%) patients TIN, 3 (12.5%) patients IgA nephropathy, 2 (8.3%) patients FSGS, 2 (8.3%) patients minimal change disease, 2 (8.3%) patients AA amyloidosis, 2 (8.3%) patients crescentic glomerulonephritis and 1 (4.2%) patient lupus nephritis. In the DKD+NDKD patient group; 2 (50%) patients had TIN, 1 (25%) patient had MN and 1

Table 1. The characteristics of patients SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; CKD-EPI, chronic kidney disease epidemiology collaboration; HbA1c, glycated hemoglobin A1c. Data are expressed as the mean ± standard deviation, the median with range and number of patients or percentages.

Patient's characteristics	Results
Age (years)	59±8 (42-75)
Sex (female/male)	26/22
Serum creatinine (mg/dl)	2.2±1.8 (0.5-7.2)
Proteinuria (g/day)	5.6±4.4 (0.182-20.6)
Serum albumin (g/dl)	2.6±0.8 (1.1-4)
Microscopic hematuria (%)	58.3
Office SBP (mmHg)	128±16 (100-160)
Office DBP (mmHg)	77±10 (60-100)
Diabetes duration (years)	9.9±8 (1-30)
Diabetic retinopathy (%)	37.5
eGFR (CKD-EPI) (mL/min/1.73m ²)	47.4±30.2 (5-107)
HbA1c (%)	7±1.3 (5-12.4)

Table 2. The characteristic of patients according to kidney biopsy findings SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, glycated hemoglobin A1c; eGFR, estimated glomerular filtration rate; ΔeGFR, change in eGFR; CKD-EPI, chronic kidney disease epidemiology collaboration; DKD, diabetic kidney disease; NDKD, non-diabetic kidney disease; NS, not significant. Data are expressed as the mean ± standard deviation, the median with range and number of patients or percentages. *(Chi-square test)

Patient's characteristics	Patients with isolated NDKD	Patients with isolated DKD	Patients with DKD+NDKD	P value
Age (years)	60 (42-75)	61 (49-71)	60 (60-66)	NS
Sex (female/male)	17/7	8/12	1/3	NS
Serum creatinine (mg/dl)	1.46 (0.5-7.2)	1.32 (0.7-6.4)	1.74 (1.1-2.5)	NS
Proteinuria (g/day)	3.680 (0.197-14.6)	5.122 (0.250-14.2)	4.440 (0.182-20.6)	NS
Serum albumin (g/dl)	2.6±0.8	2.6±0.8	2.8±1.1	NS
Microscopic hematuria (%)	62.5	55	50	NS
Office SKB (mmHg)	125±16	130±15	140±14	NS
Office DKB (mmHg)	80 (60-100)	80 (60-95)	80 (70-80)	NS
Diabetes duration (years)	6 (1-30)	10 (1-30)	12 (6-17)	NS
Diabetic retinopathy (%)	8.3	75	25	<0.05*
HbA1c (%)	6.8 (5.5-8.2)	7.1 (5.3-12.4)	5.7 (5-7.2)	NS
eGFR (CKD-EPI) (mL/min/1.73m ²)	45 (5-107)	46.5 (6-85)	44.5 (23-68)	NS
eGFR (CKD-EPI) (12 months after kidney biopsy) (mL/min/1.73m ²)	62 (8-105)	44 (6-93)	57 (34-81)	NS
ΔeGFR (CKD-EPI) (12 months after kidney biopsy) (mL/min/1.73m ²)	9.7±16.1	-1.7±16.4	12.2±10.2	0.06
Renal replacement therapy (12 months after kidney biopsy) (%)	9.5	21		NS

(25%) patient had FSGS. The characteristics of patients classified in three groups based on their kidney biopsy findings are given in Table 2. No statistically significant differences were detected between the three groups with regards to age, sex, serum creatinine, proteinuria, serum albumin, microscopic hematuria, office systolic and diastolic blood pressures, duration of diabetes, HbA1c and eGFR. Compared to the NDKD patient group, the presence of DR was significantly higher in the DKD patient group (%8.3 vs. %75, $p < 0.05$). For DKD, the positive and negative predictive values of DR were 88% and 81%, respectively (75% sensitivity, 91% specificity). At the time of kidney biopsy and 12 months after, no significant difference was observed with regards to eGFR between the three patient groups. Compared to isolated DKD patients, 12 months after kidney biopsy, a visible improvement was observed in eGFR in NDKD and DKD+NDKD patients, however, the eGFR change (Δ eGFR) was not statistically significant between the three groups ($p = 0.06$). The number of patients who developed ESKD requiring renal replacement therapy 12 months after kidney biopsy was 4 (21%) in the isolated DKD group, and only 2 (9.5%) in the isolated NDKD group.

Discussion

In this study, we reviewed retrospectively 48 kidney biopsies from patients with T2DM and found NDKD in 28 (58.3%); 24 (50%) had NDKD alone, and 4 (8.3%) had NDKD superimposed on DKD. The most common diagnoses were MN, TIN, IgA nephropathy, and FSGS. We demonstrated that the presence of retinopathy higher in the DKD patient group compared to patients who had NDKD only, strongly predicted DKD in patients with T2DM. Furthermore, patients with NDKD had slower progression to ESKD compared with patients who had DKD alone, probably due to disease specific therapies aimed at their primary etiologies.

To our knowledge, this is the first study reported that the prevalence of NDKD in type 2 diabetic patients from Turkey. In patients with T2DM, NDKD prevalence is reported in different rates, when kidney biopsy indications, geographical area and/or ethnicity are considered [3-18]. Despite advances in therapeutics, DKD is remain one of the major diabetic complications [21].

Advanced glycation end products are play a potential role in the development and progression of atherosclerosis in patients with DKD, leading to increased risk of cardiovascular morbidity and mortality [22]. As the global prevalence of diabetes increases, DKD prevalence also increases rapidly, making it one of the primary causes of ESKD. A significant part of nephrology practice today consists of DKD [1]. However, kidney biopsies of T2DM patients with kidney damage reveal the presence of a heterogeneous group of diseases, known as NDKD that can be seen alone or concurrently with DKD. Diagnosing NDKD is not possible without a kidney biopsy. Since there is no consensus approach among nephrologists on how to diagnose NDKD in T2DM, the decision of kidney biopsy depends on clinicians' judgment and when the clinical presentation is considered atypical. Rapid onset proteinuria, lack of retinopathy, presence of hematuria, active urine sedimentation findings, rapid deterioration of renal function and other cases suspicious for nephropathy secondary to systemic diseases are some of the indications for kidney biopsy. For this reason, to establish accurate diagnosis, to initiate disease-specific therapy and to improve renal function to prevent the development of ESKD, the benefits of kidney biopsy must be considered [2].

In a meta analysis involving 48 studies by Fiorentino et al., NDKD prevalence in T2DM patients are reported to vary between 3% and 82.9%. The same study reports the DKD prevalence in the range of 6.5%-94%, and DKD+NDKD prevalence in the range of 4%-45.5%. The most frequently seen NDKD types were, IgA nephropathy in 16 studies, MN in 9 studies, FSGS in 6 studies and TIN in 4 studies. Compared to studies from Europe and the United States, in the studies from Asia, IgA nephropathy was the most frequently seen condition, while in the European studies the most frequently seen NDKD was FSGS [23].

In a retrospective study including 620 patients performed in the United States, Sharma et al. reported DKD, NDKD and DKD+NDKD prevalence as 37%, 36% and 27%, respectively. In the NDKD patient group, the most frequently seen cause was FSGS (22%), followed by hypertensive nephrosclerosis (18%) and acute tubular necrosis (ATN) (17%). In the DKD+NDKD patient group, the leading cause was ATN (43%) [14]. In a study performed in China, Zhuo et al. studied the kidney biopsy results of 216 T2DM patients. In this study, the majority of the patients had pure NDKD (82.9%). Simultaneous DKD+NDKD rate was reported as 10.7%, while pure DKD rate was 6.5%. In the same study, it was observed that the main NDKD cause for patients under age 60 was IgA nephropathy, while MN and TIN were observed in patients over 60 years [13]. In a retrospective study that included 97 T2DM patients in Japan, Tone et al. reported the pure NDKD rate as 47.5% [3], while in another retrospective study in India the pure NDKD rate was reported as 42.5% [4]. In a retrospective study of 51 T2DM patients, Pallayova et al. showed that 35 (68.6%) patients had non-diabetic etiology. The most common diagnoses were interstitial nephritis (20%), progressive crescentic glomerulonephritis (14%), MN (11%) and FSGS (11%) [24]. In our study, according to the kidney biopsy findings, pure NDKD was detected in 50% of the patients. This rate is similar to the available literature. In our study, the most frequently seen cause of NDKD was MN with 29.2%, followed by TIN with 20.8% and IgA nephropathy with 12.5%. In the DKD+NDKD patient group, the most frequently seen NDKD type was TIN. There are no similar studies performed in Turkey. In previous studies, IgA nephropathy was found to be the most frequent cause in Asian populations, while it was found to be the 3rd most frequent cause in our study. The fact that this was a single center study with a low number of patients must be taken into consideration.

In one of the studies on the clinical predictors of DKD or NDKD presence, Zhuo and colleagues reported that long diabetes duration, high systolic blood pressure, high HbA1c and DR presence as DKD predictors [25]. Sharma and colleagues associated long diabetes duration with the high possibility of DKD and the lower possibility of NDKD [14]. Tone and colleagues showed that the presence of DR had the highest sensitivity (87%) and specificity (93%) for predicting DKD presence [3]. This finding was supported in a study by Pham et al. in the form of lack of DR being a strong predictor of NDKD [5]. However, in another study, Lin and colleagues showed that long diabetes duration (>10 years) and presence of DR did not exclude NDKD in T2DM patients [6]. Prakash and colleagues observed NDKD in 40% of cases with DR and DKD in 43% of the cases without DR, which suggested that the lack of DR did support NDKD, but it did not exclude DKD [16]. Pallayova and colleagues demonstrated that the predictors of NDKD in T2DM patients were absence of DR, lower HbA1c values 12 months before biopsy and greater deterioration in HbA1c prior to biopsy [24]. In our study, DR was found in 18 (37.5%) patients; 15 (75%) in the isolated DKD patient group, 2 (8.3%) in the isolated NDKD patient group, and 1 (25%) in the DKD+NDKD patient group. Also, it was shown that the sensitivity of DR in predicting DKD was 75%, and specificity 91% with a positive predictive value of 88% and a negative predictive value of 81%. At the time of kidney biopsy, no statistically significant differences were observed between the three groups with regards to diabetes duration, presence of hematuria, amount of proteinuria, HbA1c level and office systolic and diastolic blood pressures.

Recently, in a meta-analysis researchers showed that serum cystatin C is an early predictor of DKD among patients with diabetes [26]. In another study, Elewa et al. demonstrated that in DKD patients, eGFR and serum albumin had an independent and significant negative correlation with plasma chemokine (C-X-C) ligand 16 (CXCL16). This study also indicated that the serum CXCL 16 may be an indicator of kidney injury [27]. In a study by Liang and colleagues showed that urinary angiotensin converting enzyme 2 (UACE2) levels were increased in T2DM and that the UACE2 is a noninvasive indicator for the metabolic status and therapeutic response of renin angiotensin system inhibitors in DKD patients [28].

The prognostic importance of kidney biopsy and its usefulness in identifying NDKD is an important issue that must be taken into consideration in T2DM patients. Isolated DKD

patients tend to have a worse prognosis compared to NDKD patients [8, 9 15, 18]. In a study by Oh et al., during the monitoring period, ESKD rate was found to be 44% (22/50) in the DKD patient group, 18.2% (2/11) in the DKD+NDKD patient group and 12.3% (8/65) in the NDKD patient group. In the pure DKD patient group, ESKD risk factors were associated with the severity of pathological classification (percent of global sclerosis and grade of interstitial fibrosis) and some clinical predictors (eGFR and proteinuria) [9]. In our study, at the end of one-year of monitoring after kidney biopsy, no statistically significant difference was found in Δ eGFR between the three groups, while 4 cases in the DKD group (21%) and 2 cases in the NDKD patient group (9.5%) developed ESKD that required renal replacement therapy. Renal biopsies of these patients commonly revealed high interstitial fibrosis and tubular atrophy scores leading to chronic damage in >50% of the renal parenchyma.

Conclusion

This study shows that NDKD is frequent in T2DM patients, particularly, when there is lack of DR, a strong predictor of NDKD. Moreover, clinical decision alone can lead to misdiagnosis and a delay in appropriate treatment for such cases. Therefore, clinicians must consider kidney biopsy more liberally for its benefits for the patient, especially in cases where the etiology of kidney disease is unclear.

Disclosure Statement

All authors declare that they have no conflicts of interest. The authors declare no any financial interests or nonfinancial relationships.

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