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Research article

Meral Mese, Serap Yadigar, Ergün Parmaksız

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Morphological pattern of non-diabetic nephropathy in type 2 diabetes mellitus patients

University of Health Sciences, Kartal Dr Lütfi Kirdar Training Hospital, Istanbul, Turkey

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Abstract. *The aim of this study was to evaluate the contribution of kidney biopsy performed with an appropriate indication to diagnosis and treatment in diabetic patients with nephropathy.*

Methods: In this retrospective study 32 type 2 diabetes patients who underwent kidney biopsy in a single center between 2012-2019 were included. Kidney biopsy indications were determined as patients with diabetes without diabetic retinopathy and with proteinuria above 1 g/day.

Results: Diabetic (DN) and non-diabetic (NDN) nephropathies were diagnosed with renal biopsy. In 14 (43.7%) of 32 patients, NDN was reported in histopathological evaluation. Membranous nephropathy was detected in 4 of these patients, focal segmental glomerulosclerosis (FSGS) in the other 4 patients, light chain disease in 2 patients, IgA nephropathy in 2 of the patients, minimal change nephropathy in another patient, and finally AA amyloid in one patient. NDRD seen superimposed on DN (DN + interstitial nephritis and DN + FSGS) was observed in 2 patients. DN was detected in 16 (50%) of 32 type 2 diabetic patients.

Conclusion: Kidney biopsy in patients with type 2 diabetes is an important tool for diagnosing NDN, choosing the right treatment tactics and determining kidney prognosis.

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Correspondence should be addressed to Serap Yadigar: serapsert2000@yahoo.com

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Мерал Месе, Серап Ядігар, Ергун Пармаксіз

Морфологічний патерн недіабетичної нефропатії у хворих на цукровий діабет 2 типу

Університет наук про здоров'я, навчальний госпіталь ім. Карталя Лютфі Кірдара, Стамбул, Туреччина

Резюме. *Метою цього дослідження було оцінити внесок біопсії нирки у діагностику та лікування хворих на цукровий діабет з нефропатією.*

Методи. У це ретроспективне дослідження було включено 32 пацієнти з цукровим діабетом 2 типу, яким була проведена біопсія нирки в одному центрі в період з 2012 по 2019 роки. Показаннями до біопсії нирки були цукровий діабет без діабетичної ретинопатії та протеїнурія понад 1 г/добу.

Результати: Діабетична (ДН) та недіабетична (НДН) нефропатії були діагностовані за допомогою біопсії нирки. У 14 (43,7%) із 32 пацієнтів під час гістопатологічного дослідження виявлено NDN. Мембранозна нефропатія була діагностованою у 4 пацієнтів, фокальний сегментарний гломерулосклероз (ФСГС) - у 4 пацієнтів, хвороба легких ланцюгів у 2 пацієнтів, IgA нефропатія у 2 пацієнтів, нефропатія мінімальних змін у 1 пацієнта та АА амілоїдоз у 1 пацієнта. Подвійний патерн НДН та ДН (ДН + інтерстиціний нефрит та ДН + ФСГС) спостерігався у 2 пацієнтів. ДН виявлено у 16 (50%) із 32 хворих на цукровий діабет 2 типу.

Висновки. Біопсія нирки у хворих на цукровий діабет 2 типу є важливим інструментом діагностики НДН, вибору правильної тактики лікування та визначення прогнозу.

Ключові слова: *діабетична нефропатія, недіабетична нефропатія, біопсія нирки, гломерулонефрит, протеїнурія.*

Introduction. Diabetes is a global epidemic disease and the number of patients worldwide is growing rapidly. Currently, there are about 500 million people affected by diabetes mellitus worldwide. It is expected that by the year 2045, this number will have increased to about 693 million. Diabetic nephropathy (DN) is one of the major complications of diabetes [**1**]. In addition, diabetic nephropathy is the most common cause of chronic kidney failure and end-stage kidney disease in the world. Despite improvements in the follow-up of diabetic patients, the frequency of DN has not decreased in the last 30 years [**2**].

Early developing proteinuria (<5 years), rapid impairment of kidney function, impaired kidney function without distinct proteinuria, and detection of active urine sediment incompatible with the nature of DN should suggest the presence of non-diabetic nephropathy (NDN). In addition, age, absence of retinopathy, microhematuria and subnephrotic proteinuria and short-term history of diabetes suggest the possibility of NDN in type II diabetics, but their effects have varied in various studies [**3, 4**]. Although kidney biopsy is a gold standard for diagnosis, the biopsy is not performed in most patients since the diagnosis is based on clinical, end-organ damage (retinopathy, neuropathy, proteinuria) and laboratory findings with an ongoing traditional approach. However, although this approach is adequate for type I diabetes, it is not clear for type II. Diabetic kidney disease is known to be clinically and pathologically heterogeneous in these patients. The nature and prevalence of NDN differ in studies. On the other hand, while changes in diabetic nephropathy are irreversible; some non-diabetic nephropathies, such as interstitial nephritis, membranous nephropathy, or minimal change disease, can often be treated. Therefore, it is essential to detect NDN in diabetic patients [**5, 6**].

Classical diabetic glomerulopathy is characterized by, glomerular basement membrane thickening, endothelial damage, mesangial enlargement and the presence of mesangial nodules and loss of podocytes. However, besides classical glomerulopathy, glomerular lesions and tubulointerstitial disease can also be detected in diabetes. In type 1 diabetes with albuminuria for five years or more, the cause of diabetic kidney disease is most likely diabetic nephropathy while the variety is higher in type 2 diabetics due to the possibility of superimposed or de novo nondiabetic kidney disease. A definitive diagnosis can only be made by kidney biopsy. As a result of many studies, it has been determined that non-diabetic kidney disease is seen between 27- 79% of diabetic patients [**7-10**].

In general, in the presence of long-standing diabetes, especially if there is retinopathy, it is assumed that the cause of chronic kidney failure is diabetic nephropathy [**11**]. While the absence of retinopathy in kidney biopsy studies supports possible non-diabetic nephropathy, especially the presence of severe pro-

Serap Yadigar
serapsert2000@yahoo.com

liferative diabetic retinopathy supports diabetic nephropathy [12-15]. However, there were still many conditions in that DN was not associated with diabetic retinopathy (DR), and the incidence of fundus lesions was inconsistent in different studies [16, 17]. Although the purpose of kidney biopsy is diagnostic, prognostic information could be obtained through the evaluation of the class of glomerular disease and the degree of interstitial fibrosis. In a large study results showed that most of the patients had significant renal dysfunction, with median creatinine of 2.5 mg/dl (IQR, 1.6–4.4) and eGFR 29.1 ml/min per 1.73 m^2 (IQR, 14.5–54.5) at time of biopsy; just over half of the patients had eGFR <30 ml/min per 1.73 m^2. Moreover, the median proteinuria for the entire cohort was in the nephrotic range. NDN was identified in >60% of biopsies: 220 patients with NDN alone and 164 patients with NDN and superimposed renal disease [18].

This study aims to determine the prevalence and independent determinants of NDN in follow-up type II diabetic patients in our center and to determine the effect on prognosis in patients with type 2 diabetes.

Materials and Methods. The study was a retrospective case-controlled study of type 2 diabetic patients treated at Kartal Dr. Lutfi Kirdar City Hospital. The study protocol was approved by Kartal Dr L tfi K rdar City Hospital's Ethical Committee (approval no: 2020.514.172.1 approval date: 26.02.2020).

Thirty-two type 2 diabetic patients who underwent kidney biopsy in our hospital between 2012-2019 were included in the study. Type 2 diabetic patients who have proteinuria of 1gr> day without any diabetic retinopathy were included in the study. Exclusion criteria were as follow: insufficient medical data, unqualified biopsy material, presence of diabetic retinopathy without any signs of superimposed glomerular disease (rapidly increase in creatinine level, ANCA seropositivity and persistent hematuria), stage 4 or 5 kidney failure, and patients with a kidney transplant.

Demographic data of patients, clinical information (duration of diabetes, accompanying diseases, e.g. hypertension, coronary artery disease, type of antidiabetic medication), laboratory test results (level of proteinuria in 24 hrs urine, presence of hematuria in urine, blood urea, creatinine, albumin, hemoglobin A1c levels) were gathered. Diabetic retinopathy was assessed by a specialist ophthalmologist.

All renal biopsy samples were evaluated by a nephropathologist with standard light microscopy and immunofluorescence. Electron microscopy (EM) is not routine in our center, thus it is not used for diagnosis The pathological diagnostic criteria of diabetic nephropathy were thickening of the glomerular basement membrane (> 395nm in women and > 430nm in men) and mesangial enlargement with or without nodular glomerulosclerosis.

Statistical Analysis. Groups' gender, application complaint, age of diabetes, insulin requirement, additional diseases, amount of proteinuria, presence of hematuria, urea creatinine, albumin, hemoglobin A1c values are presented as numerical data mean ± standard deviation, median (minimum-maximum) and categorical data number (frequency percentage). Patients were divided into two groups: non-diabetic nephropathy (group1) and diabetic nephropathy (group2) according to kidney biopsy results. The distribution of each group was checked with the Kolmogorov-Smirnov test and histogram. Normally distributed numerical data were compared with the Student t-test and non-normally distributed data were compared with the Mann Whitney U test. Categorical data compared with Pearson Chi-square and Fisher Exact test. $P < 0.05$ was considered statistically significant. All statistical analyses were made using the Jamovi program (Version 1.2) [19].

Results. In the present study, the number of men and women was equal. The mean age of the patients was 52 years (range, 41-67 years), the duration of diabetes was 10 years (range, 3-16 years), and the mean creatinine values were 1.6 mg/dl (range, 0.64-3.4 mg/dl). In the groups 81% (n = 26) of our patients were using insulin and 34.4% (n = 11) had accompanying coronary artery disease.

In 14 of 32 patients, NDN was reported in histopathological evaluation. Membranous nephropathy was detected in 4 of these patients, focal segmental glomerulosclerosis (FSGS) in the other 4 patients, IgA nephropathy in 2 of the patients, and light chain disease in 2 patients, minimal change nephropathy in another patient, and finally AA amyloid in one patient. NDRD seen superimposed on DN (DN + interstitial nephritis and DN + FSGS) was observed in two patients. These 2 patients were included in the NDN group during statistical analysis. In our study totally 16 of 32 patients were shown to have NDN (NDN Group). The rest of the 16 patients were named as DN Group.

Demographic and clinical and laboratory features according to the groups are given in Table 1.

Table 1

Clinical and laboratory characteristics of nephrotic and non nephrotic groups

	Nondiabetic nephropathy		Diabetic nephropathy		P
	Nephrotic (n=9)	Non-nephrotic (n=7)	Nephrotic (n=11)	Non nephrotic (n=5)	
Age	52.33 (49-67)	53.57(41-62)	50.63 (42-63)	48.2(44-53)	0.589
Diabetes year	7.2 (5-15)	7.71(4-15)	13.18 (8-16)	12.4 (10-15)	0.003

Continuation of Table 1

	Nondiabetic nephropathy		Diabetic nephropathy		P
	Nephrotic (n=9)	Non-nephrotic (n=7)	Nephrotic (n=11)	Non nephrotic (n=5)	
HbA1c	7.07 (5.9-9.5)	7.9 (7.9-10)	7.8 (5.7-8.8)	8.6 (6.6-11)	0.133
Creatinin(mg/dl)	1.32 (0.6-2.6)	1.72 (0.8-1.2)	1.9 (0.9-3.1)	1.78 (0.7-2.4)	0.246
Albumin(gr/L)	3.81 (3.1-4.4)	3.91 (3.5-4.6)	3.51(3.2-3.8)	3.76(3.4-4.1)	0.089

Student t-test and Mann Whitney U test were used to compare the groups.

Among the parameters evaluated HbA1c levels ($p<0.015$) and the duration of diabetes ($p<0.01$) were higher in the DN group. Also, the mean serum albumin level was lower in the DN group ($p = 0.027$). There was no statistically significant difference between the groups according to the other data ($p > 0.05$)

Both groups were subgrouped as nephrotic and non-nephrotic proteinuria and evaluated separately (Table 2).

Table 2

Clinical and laboratory characteristics of diabetic and nondiabetic nephropathy groups

	Total	Diabetic	Nondiabetic	p
Age	51.375±6.676	50.294±5.966	52.60±7,613	0.345
Gender(male), n (%)	16 (50)	10 (62.5)	6 (37.5)	0.157
Diabetes time, (year)	10.19±4.295	13.5 (8-16)	6 (3-15)	<0.001
nsulin use, n (%)	17 (53.1)	10 (62.5)	7 (43.8)	0.288
Oral antidiabetic drug use, n (%)	15 (46,9)	7 (41.2)	8 (53,3)	0.78
HbA1c (%)	7.775±1.284	8.282±1.195	7.2±1.172	0.015
Coronary a. disease n (%)	11 (34.4)	7 (43.8)	4 (25)	0.264
Thyroid disfunction n(%)	11 (34.4)	7 (43.8)	4 (25)	0.264
Dialysis need, n (%)	7 (21.9)	5 (31.3)	2 (12.5)	0.394
Proteinuria (g/24h)	4.334±1.883	4.500±2.193	4.186±1.615	0.645
Hematuria n (%)	26 (81.3)	12 (75)	14 (87.5)	0.654
Creatinin (mg/dl)	1.682±0.734	1.800±0.730	1.549±0.739	0.343
Total protein (g/l)	6.834±0.335	6.859±0.264	6.807±0.409	0.668
Albumin (g/l)	3.725±0.377	3.588±0.254	3.880±0.439	0.027

Kruskal Wallis test was used to calculate p-values.

The longest diabetes duration and the highest creatinine values were found in the nephrotic DN group. Contrary to this, the mean HbA1c level was higher in the non-nephrotic DN group. The lowest duration of diabetes, the lowest mean HbA1c values and the lowest mean creatinine values were found to be in the nephrotic NDN group.

While patients in the isolated DN group received conservative treatment, patients in the NDN group were treated according to the underlying disease. During the follow-up period, 5 patients in the DN group and 2 patients in the NDN group needed dialysis. Two patients in the NDN group and 1 patient in the DN group passed away. The follow-up of other patients continues in the nephrology outpatient clinic.

Discussion. Information on NDN development mechanisms is inadequate and speculative. Recent pieces of information suggest that hyperglycemia, glycolysis end products, immune complexes, and biochemical changes in diabetes activate kidney cells by causing increased cell adhesion molecules and pro-inflammatory cytokines through protein kinase [20]. Some proteins that have been altered in diabetes have the potential to trigger inflammation such as oxidized LDL. Immune complexes and glomerular IgG deposits (especially proinflammatory IgG1 and IgG3) were detected in experimental models of diabetes. Exposure to antigenic compounds and glomerular changes may cause an immune reaction in the subepithelial are [21]. However, some authors found no difference in the fre-

quency of NDN in patients with and without diabetes, and argued that glomerulonephritis detected in the diabetic kidney is only a coincidence [22].

It is often made a clinical diagnosis of diabetic nephropathy when diabetic patients have retinopathy and proteinuria. Therefore diabetic patients did not receive renal biopsy until they are suspected to have NDN. Unfortunately, there is no available guideline on which diabetic patient should receive a kidney biopsy. Although DN is generally considered to exist during the development of microalbuminuria in patients with type I diabetes, the probability of having NDN or mixed glomerulopathy should be considered in patients with type II diabetes. Many studies have found a strong relationship between diabetic retinopathy and nephropathy [23]. The presence of diabetic nephropathy in 44-70% of diabetic patients without retinopathy indicates that the likelihood of DN should not be ignored in the absence of retinopathy, but the absence of retinopathy may be a strong indicator of NDN [24]. In our study, patients without diabetic retinopathy were selected and it was noteworthy that the kidney biopsy results in the group with a long duration of diabetes was related to diabetic nephropathy.

In most regression studies, nondiabetic nephropathy was found to be associated with an absence of retinopathy and a short duration of diabetes. Therefore, it will be appropriate to perform a kidney biopsy in this group of patients in order not to skip an underlying non-diabetic glomerular disease. In our study, the detection of 43.75% NDN and 6.25% mixed nephropathy in the biopsy results of type II diabetic patients without diabetic retinopathy supports the importance of biopsy in this group of patients.

The specificity of microscopic hematuria and active urinary sediment for the diagnosis of NDN in the diabetic patient group is 93.1% to 100% and the positive predictive value is 81% to 100%. Some studies have suggested that in typical diabetic glomerulopathy, hematuria can be detected at a rate of 35-78%, so it is not useful for the diagnosis of NDN (26). Dysmorphic RBCs in the urine sediment may be more useful than microhematuria for indicating NDRD [25]. In our study, hematuria was found in 12 (75%) of 16 patients in the group with diabetic nephropathy and 14 (87.5%) patients in the NDN group. In addition, the duration and severity of hyperglycemia, hyperlipidemia, hypertension and proteinuria are also known risk factors for diabetic nephropathy. In a single-center study a diagnostic model which may be valuable to physicians- was developed based on logistic regression featuring six variables (ie, anemia, eGFR levels, DR, proteinuria, hypertension, and DM) which can effectively discriminate between DN and NDRD with 93.2% sensitivity and 82.6% specificity [26].

After all, with the latest evidence, the traditional clinical course of diabetes is changing. Studies show that the development of proteinuria and the reduction in eGFR may have independent pathogenesis rather than a consequence. This phenomenon may be caused by the widespread use of drugs that block the renin-angiotensin systems and develop glycemic control [27]. As the traditional clinical course of diabetes continues to change, the prevalence of isolated DN patients with severe proteinuria will decrease, while those with NDN will increase proportionally. As a result, renal biopsy will be considered more intensively in this group. The prognosis of diabetic patients with non-diabetic nephropathy is significantly better than that of patients with diabetes-proven diabetic nephropathy. In patients with isolated DN, the risk of progression to ESRD is between 30 and 60% within 3 years of pathological diagnosis. The risk is less than 10% in NDN cases, whereas it is similar to DN in mixed cases [7]. Since there are no globally accepted diagnostic guidelines, the most accurate approach in this patient group would be to perform intermittent re-evaluation and renal biopsy when necessary [24-28].

The present study has several limitations. Patients with advanced-stage kidney failure without diabetic retinopathy were not included in this study. This group of patients is perhaps the most unlucky group who lost the chance of treatment due to the possibility that the diagnosis of non-diabetic nephropathy was missed. Therefore, a biopsy could be re-evaluated either periodically or when clinical condition changes (e.g; increasing urinary RBC count). Another limitation of our study is the low number of patients. Studies with a broader and larger number of patients may change the traditional approach to diabetic kidney patients in the future.

Conclusion. The present study showed that NDN (alone or superimposed with DN) was detected in 50% of 32 diabetic patients without diabetic retinopathy. The nephrologist should consider if NDN is potentially present in diabetic patients and the risk/benefit ratio of biopsy. Kidney biopsy in patients with type 2 diabetes is an important tool for diagnosing NDN, choosing the right treatment tactics and determining kidney prognosis.

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