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Non-Diabetic Kidney Disease in Patients with Type 2 Diabetes Mellitus–11-Year Experience from a Single Center

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ABSTRACT

Introduction: In patients with diabetes mellitus (DM), non-diabetic renal disease (NDRD) can also occurs, as well as diabetic nephropathy. NDRD is most accurately diagnosed using kidney biopsy. **Aim:** The aim of the study was to investigate the incidence and type of NDRD diagnosed by kidney biopsy in patients with type 2 DM and the correlation of clinical and laboratory findings with histopathological diagnosis. **Material and Methods:** From April 2007 to October 2018, 290 kidney biopsies were performed at the Department of Nephrology, Internal Medicine Clinic in Banja Luka, out of which 18 patients (males 9, mean age 59.8 years) were with type 2 DM. The US-guided (ultrasound device: Toshiba Famio 5) kidney biopsy was performed using an automatic biopsy instrument FAST-GUN® with needle 16G. Kidney tissue samples were analyzed by light microscopy and immunofluorescence. **Results:** In 18 patients with type 2 DM, the average duration of the disease was 5.9 years, 5 patients had a retinopathy, and 16 patients had hypertension. Biopsy indications were: nephrotic syndrome in 11 patients, asymptomatic urinary abnormalities in 3 patients, and rapid chronic renal failure progression. Unsatisfactory quality sample for pathohistological analysis was obtained in one patient, and out of the other 17, 6 (35.3%) had NDRD, 3 (17.6%) had NDRD superimposed with the diabetic nephropathy, and 8 (47.1%) had diabetic nephropathy. Of the patients who had NDRD, 3 had membranous glomerulonephritis, 1 had focal segmental glomerulosclerosis, and two had hypertensive nephroangiosclerosis. Out of patients with coexisting NDRD and diabetic nephropathy, 2 had hypertensive nephroangiosclerosis and one diabetic nephropathy and lupus nephritis. **Conclusion:** NDRD was diagnosed using kidney biopsy in 9/17 patients with type 2 DM, which confirms the significance of the kidney biopsy in patients with DM with properly indications. Accurate diagnosis provides disease specific treatment and thus significantly improves the long-term prognosis of the patient.

Keywords: Diabetes mellitus, Kidney biopsy, Diabetic nephropathy, Non-diabetic renal disease.

1. INTRODUCTION

In the last decades, diabetic nephropathy has become the leading cause of end-stage kidney disease worldwide (1). The increase in the number of patients with ESKD caused by diabetic nephropathy is the consequence of a constant increase in the prevalence of diabetes mellitus (DM), especially type 2 DM, which is 10 times more frequent than type 1, as well as prolongation of the life expectancy of diabetic patients who experience such late complications (2).

Diabetic nephropathy is not the only form of renal disease in patients with DM, but other non-diabetic renal diseases can occur: glomerular (membranous nephropathy), tubulointerstitial or vascular diseases. The timely diagnosis of non-diabetic renal disease is of great importance for early etiological treatment of patients, which can significantly slow down or completely stop the progression of chronic kidney disease to end-stage renal failure (3) .

Many forms of non-diabetic kidney disease can be successfully treated (e.g. glomerulonephritis with immunosuppressives therapy), in contrast to diabetic nephropathy, which in the developed form with manifest proteinuria has frequently progressive course and leads to end-stage renal failure in a large percentage. Therefore, it is very important to diagnose non-diabetic kidney dis-

ease in patients with DM, as this significantly improves the prognosis of the disease (3) .

Kidney biopsy is a gold standard in diagnosing non-diabetic renal disease in diabetic patients; it is a guidepost for treatment, and a prognostic indicator, too. Kidney biopsy can find out that a patient has: a) diabetic nephropathy, b) coexisting diabetic nephropathy and other non-diabetic renal disease (usually glomerulonephritis), c) only non-diabetic renal disease.

Indications for renal biopsy in patients with diabetes are (4) :

* Nephrotic syndrome in patients who had diabetes for less than 5 years or without accompanying diabetic retinopathy, or with sudden worsening of proteinuria;

* Asymptomatic urinary abnormalities–microscopic or gross hematuria in patients with diabetes, which are less common clinical manifestations of diabetic nephropathy, especially in the presence of red blood cell casts or granular casts characteristics of glomerulonephritis;

* Acute renal failure;

* Clinically unclear sudden deterioration of chronic kidney failure in patients with diabetes (4) .

KDOQI Clinical Practice Guidelines from 2007 suggest clinical features that can be indicative of the presence of non-diabetic renal disease in diabetic patients: absence of diabetic retinopathy, rapidly deteriorating renal function, proteinuria of increasing severity, or nephrotic syndrome development, refractory hypertension, active urinary sediment (microscopic hematuria with red blood cell or granular casts), signs or symptoms of systemic disease or GFR decline of > 30% within two to three months (5) .

2. AIM

The aim of the study was to investigate the incidence and type of non-diabetic kidney disease diagnosed by kidney biopsy in patients with type 2 DM, to analyze the laboratory and clinical findings, and to evaluate the correlation of clinical and laboratory findings with histopathological diagnosis.

3. MATERIALS AND METHODS

From April 2007 to October 2018, 290 ultrasound-guided kidney biopsies were performed at the Department of Nephrology, Internal Medicine Clinic in Banja Luka, out of which 18 patients (male/female: 9/9, mean age: 59.8 years 40-78)) were with type 2 diabetes mellitus.

The kidney biopsy was performed using an automatic biopsy instrument FAST-GUN® with a hollow probe guide, needle 16G. Kidney biopsy was ultrasound-guided (ultrasound device Toshiba Famio 5) and lower pole of the left kidney was punctured. Two kidney biopsy specimens were obtained; one sample was analyzed using light microscopy, and the other was taken for immunofluorescence microscopy. Pathohistological analysis of kidney tissue was done initially at the Institute of Pathology, Clinical Center of Serbia and for the past 8 years at the Clinic for Pathology of the University Clinical Center in Banja Luka.

Before the biopsy a detailed evaluation of patient was done. It included medical history, physical exam, abdominal ultrasound, chest radiography and, if necessary, other imaging methods. Laboratory blood tests included erythrocyte sedimentation rate (ESR), full blood cell count, serum glucose, bilirubin, transaminases, LDH, urea, creatinine, acidum uricum, electrolytes. In addition, HbA1c, protein electrophoresis, tumour markers, hepatitis virus screen, and autoimmune disease screen–complement levels (C3 and C4), antinuclear antibody (ANA), anti-double-stranded DNA (anti-dsDNA), cANCA, pANCA were also determined. Urinalysis included albuminuria and proteinuria detecting and quantifying in 24-hour urine, as well as urinary sediment analysis and urine culture. In addition, funduscopy was performed in all patients, as well gynecological exam for females, and urology exam for males.

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 20.0 (SPSS Inc, Chicago, Ill, USA). Descriptive statistical methods were used. For metric data, arithmetic mean and standard deviation were used. ANOVA test was used to compare variable of the three groups (mean values). Also quantification of the association between variables expressed by Spearman"s correlation (Shapiro-Wilk test) was performed. Statistical significance was set P value of<0,05 (2-tailed).

4. RESULTS

The demographic, clinical data and biochemical parameters on patients with type 2 diabetes who have undergone biopsy are shown in Table 1. Before the kidney biopsy, the proteinuria level was in range 1.2 to 33 grams per day. The average duration of diabetes was 5.9 years

Patient	Age (year)	Gender	Duration of disease, years	Diabetic retinopathy	Hypertension	Proteinuria, g/day
1.	45	F	5	no	yes	5.16
2.	67	F	2	no	yes	10.6
3.	43	M	2	no	no	4.7
4.	62	M	4	no	yes	1.2 g
5.	63	F	7	no	yes	14
6.	60	F	2	no	yes	7.16
7.	63	F	18	yes	yes	10
8.	46	M	3	no	yes	8.9
9.	40	F	6	yes	yes	5.96
10.	61	M	11	yes	yes	13.8
11.	45	M	3	no	yes	2
12.	57	F	7	yes	no	11.8
13.	76	M	0.33	no	yes	14.8
14.	61	M	2	no	yes	9.3
15.	78	F	9	no	yes	8.6
16.	69	M	5	no	yes	7.28
17.	57	F	1	no	yes	10.1
18.	51	M	16	yes	yes	33

Table 1. Demographic data and clinical and biochemical parameters by patients with type 2 diabetes who have undergone kidney biopsy. M-male, F-female

Patient	Indications for kidney biopsy	Pathohistological findings
1.	Nephrotic syndrome	Membranous glomerulonephritis
2.	Nephrotic syndrome, ANA+, diabetes mellitus duration < 2 years	Lupus nephritis + diabetic nephropathy
3.	Nephrotic syndrome, diabetes mellitus duration < 2 years	Diabetic nephropathy stage 2
4.	Diabetes with borderline blood sugar leveles for 4 years, proteinuria for about 1 year, potentially kidney donor for her/his son	Diabetic nephropathy stage 2 (contraindication for donor)
5.	Extensive nephrotic syndrome (acute-onset)	Diabetic nephropathy stage 3
6	Nephrotic syndrome, diabetes mellitus duration 2 years	Diabetic nephropathy stage 2
7.	Nephrotic syndrome, anti-dsDNA+	Diabetic nephropathy + hypertensive nephroangiosclerosis
8.	Nephrotic syndrome, diabetes mellitus duration 3 years	Diabetic nephropathy stage 3
9.	Nephrotic syndrome and rapidly deterioration of chronic kidney disease (CKD)	Diabetic nephropathy stage 2
10.	Nephrotic syndrome, acute-onset	Diabetic nephropathy stage 3
11.	Rapidly deterioration of CKD	Diabetic nephropathy + hypertensive nephroangiosclerosis
12.	Dysmorphic erythrocytria, ANA + diabetic retinopathy	Membranous glomerulonephritis
13.	Nephrotic syndrome, diabetes mellitus duration 4 months	Focal segmental glomerulosclerosis (FSGS)
14.	Nephrotic syndrome, diabetes mellitus duration 2 years	Appropiate tissue sample was not obtained.
15.	Nephrotic syndrome, acute-onset; microscopic hematuria	Hypertensive nephroangiosclerosis
16.	Nephrotic syndrome, CKD deterioration	Hypertensive nephroangiosclerosis
17.	Nephrotic syndrome, microscopic hematuria	Membranous glomerulonephritis
18.	Nephrotic syndrome, rapidly deterioration of chronic kidney disease (CKD)	Diabetic nephropathy stage 2

Table 2. Indications for biopsy and pathohistological diagnosis. CKD-chronic kidney disease; ANA-antinuclear antibody; anti-dsDNA-anti double-stranded DNA

(from 4 months to 18 years); 5 patients had retinopathy, and 16 patients had hypertension.

Indications for renal biopsy in our patients with diabetes were: suddenly or acute-onset nephrotic syndrome in 11 patients who had diabetes for less than 5 years or some positive immunological findings; rapidly deterioration of chronic renal failure in 4 patients; asymptomatic urinary abnormalities (persistent proteinuria and/or microscopic hematuria) in 3 patients (Table 2).

In one patient hematoma (diameter about 5 cm) after biopsy happened, accompanied with blood loss (blood count) that required transfusion of 2 units of blood (major complication) but an active urological intervention had not to be performed. All other kidney biopsies were performed without complications. Representative samples were obtained in 17 patients, and pathohistological diagnosis could be established. In one patient obtained sample was not sufficiently representative to establish a pathohistological diagnosis.

Parameters	NDRD N=6	NDRD + DN N=3	DN N=8	P
Patient's age at biopsy time	63.7± 12.8	58.3±11.7	53.2 ±9.4	0.494
Average DM duration, years	4.6 ± 3.4	7.6 ± 5.5	6.4 ± 4.9	0.026
Proteinuria, g/day	9.6 ± 3.4	7.5± 4.8	11.1 ±9.9	0.02
Serum creatinine, µmol/L	119.8 ±48.9	138.3 ±123.5	170.0± 103.9	0.288
Blood glucose,mmol/L	6.7 ±1.8	7.8 ± 1.3	8.1± 3.0	0.270

Table 3. Main demographic features and biochemical parameters of the 17 patients with type-2 diabetes mellitus, included in the study, that were divided into three groups based on the renal biopsy findings: diabetic nephropathy (DN), nondiabetic renal disease (NDRD) and DN + NDRD groups. NDRD–nondiabetic renal disease, DN–diabetic nephropathy

	Number of patients	DN	NDRD	Average duration of DM
Galešić et al. [2]	11	4 (36.4%)	7 (63.6%)	6.5 years
Ghani et al. [6]	31	17 (54.8%)	14 (45.2%)	9.33 years
Yum et al. [7]	18	10 (56%)	8 (44%)	Not specified
Castellano et al. [8]	20	9 (45%)	11 (55%)	Not specified
Mak et al. [9]	51	34 (67%)	17 (33%)	Not specified
Prakash et al. [10,11]	260	228 (87.7%)	32 (12.3%)	<5 g 43.7% 5–9g – 25% >10g– 31.2%
Zhuo et al. [12]	244	223 (92.2%)	19 (7.8%)	Not specified
Yaqub et al. [13]	68	23 (31%)	45 (69%)	9 years
Lakshminarayana [14]	60	15 (25%)	45 (75%)	8.7 years
Shujun Liu [15]	273	68 (24.9%)	205 75.1%)	4.3 years
Wagrowska-Danielewitz [3]	76	27 (35%)	49 (65%)	8.4 years
Imtiaz S.[16]	206	74 (36%)	132 (64%)	6.8 years

Table 4. Results of kidney biopsy in patients with diabetes according to several authors in the world. DN–diabetic nephropathy, NDRD–non-diabetic renal disease (alone or coexisting with diabetic nephropathy)

Indications for biopsy and histopathological findings in kidney tissue samples obtained from 17 patients are shown in Table 2. Diagnosis of diabetic nephropathy was established in 8 patients. Of these 8 patients, 5 were diagnosed with diabetic nephropathy stage 2–(mesangial proliferation) and 3 patients had classical nodular glomerulosclerosis (the Kimmelstiel-Wilson lesion); diabetic nephropathy, stage 3. The finding of diabetic nephropathy with coexisting kidney disease was established in 3 patients–in two cases there was association of diabetic nephropathy with hypertensive nephroangiosclerosis, and the third case with lupus nephritis.

Isolated non-diabetic renal disease was diagnosed in 6 patients–in 3 patients membranous glomerulonephritis, in 1 patient focal segmental glomerulosclerosis, and in 2

patients hypertensive nephroangiosclerosis. Histopathological analysis of kidney tissue samples obtained from 17 patients showed that 9 (52.9%) patients had non-diabetic kidney disease–in 6 (35.3%) patients NDRD was alone, without signs of diabetic nephropathy, and in 3 (17.6%) patients NDRD was superimposed on diabetic nephropathy. In the remaining 8 (47.1%) patients diabetic nephropathy was diagnosed. Of the 5 patients who had diabetic retinopathy, there was another indication for renal biopsy (sudden nephrotic syndrome, impaired renal function), 4 patients had diabetic nephropathy and 1 patient had isolated non-diabetic renal disease (membranous glomerulonephritis). Of the 12 patients who did not have diabetic retinopathy, even 8 had an isolated or coexisting non-diabetic kidney disease. The average duration of diabetes in patients with non-diabetic kidney disease was 4.55 years, in patients with coexisting diabetic nephropathy and non-diabetic renal disease the average duration of diabetes was 7.6 years, among which was a patient who had diabetes for 18 years and had pathohistologically diagnosed diabetic nephropathy associated with hypertensive nephroangiosclerosis. In patients with diabetic nephropathy, the average duration of diabetes was 6.4 years. Main demographic features and biochemical parameters of the 17 patients with type 2 diabetes mellitus included in the study, that were divided inti three groups based on the based on the renal biopsy findings: diabetic nephropathy (DN), non-diabetic renal disease (NDRD) and DN + NDRD groups are shown in Table 3. In the diabetic nephropathy group proteinuria was significantly more severe than in diabetic nephropathy with coexisting non-diabetic nephropathy and non-diabetic nephropathy group: 11.1±9.9 g/day vs. 7.5 ± 4.8 g/day and 9.6±3.4 g/day, respectively (p =0.002) and the duration of DM was significantly longer (6.4 ± 4.9 years vs. 7.6 ± 5.5 years and 4.6 ± 3.4 years, respectively (p = 0.02) than in the NDRD group. In the group NDRD+DN duration of diabetes mellitus was significantly longer than in diabetic nephropathy (DN) group and in non diabetic nephropathy group(NDRD): 7,7±5,5vs 6,4±4,9vs 4,6±3,4years. In a patient with lupus nephritis and diabetic nephropathy, immunosuppressives therapy with mycophenolate mofetil and median doses of prednisolone was administered for 12 months. Then, mycophenolate mofetil therapy was discontinued and prednisolone dose was slowly tapering until complete discontinuation. All the time, the patient was taking ACE inhibitors, and glycemic control was achieved by switching from oral antidiabetics to insulin therapy. This therapy enabled achievement of a partial remission of nephrotic syndrome, with preserved renal function during a three-year follow-up monitoring.

In two patients with primary membranous glomerulonephritis, immunosuppressives therapy with cyclophosphamide and prednisolone was administered and partial disease remission with preserved renal function was achieved. A complete disease remission has been achieved with prednisolone and cyclophosphamide combination therapy in a patient with focal segmental glomerulosclerosis. In patients with concomitant diabetic therapy and hypertensive nephroangiosclerosis, glycemic control with strict blood pressure control was performed.

5. DISCUSSION

Kidney biopsy was performed in 18 patients with type 2 diabetes mellitus, and appropriate kidney tissue specimens were obtained from 17 patients. Pathohistological analysis revealed non-diabetic renal disease in 6 (35.3%) patients, coexisting non-diabetic renal disease and diabetic nephropathy in 3 (17.6%) patients (the overall percentage of non-diabetic kidney disease was 52.9%), and diabetic nephropathy in 8 (47.1%) patients. Out of patients who had non-diabetic renal disease, three had membranous glomerulonephritis, one had focal segmental glomerulosclerosis, and two had hypertensive nephroangiosclerosis. Out of patients with coexisting non-diabetic kidney disease and diabetic nephropathy 2 had hypertensive nephroangiosclerosis and one had diabetic nephropathy and lupus nephritis. A partial or complete remission was achieved in patients with glomerular disease with or without diabetic nephropathy using immunosuppressives therapy.

Patients with diabetes may, in addition to diabetic nephropathy have non-diabetic renal disease, most often some of the glomerulonephritis that can be successfully treated. Proportion of non-diabetic renal disease in patients with diabetes is different in published studies (Table 4). Several indicators can help in the clinical differentiation of diabetes and non-diabetic renal disease. The clinical course of non-diabetic renal disease is atypical, with the absence of changes in the target organs caused by long-term diabetes (retinopathy), usually more abundant proteinuria that occurs after a shorter duration of diabetes than in diabetic nephropathy, and the presence of dysmorphic erythrocytes and erythrocyte casts in urine indicating glomerulonephritis.

Various authors showed the different incidence of the disorders that may indicate diabetic nephropathy or non-diabetic renal disease. Thus, in several studies and two meta-analyzes, a statistically significant correlation between the presence of diabetic retinopathy and the pathohistological finding of diabetic nephropathy has been shown (16-20), but there are also studies that indicate that there is no statistically significant correlation between findings of diabetic retinopathy and the histopathological findings of diabetic nephropathy (9, 11). Yaqub et al. (13) as well as Chong et al. (19) described that in diabetic patients with performed kidney biopsy significantly lower duration of diabetes was found in patients with non-diabetic renal disease than in those with diabetic nephropathy. The average duration of diabetes in our patients was somewhat shorter in comparison with data of most authors and similar to the disease duration described by Huyun Liu et al. (15). In some of our patients, diabetic nephropathy was diagnosed pathohistologically, although the duration of diabetes was shorter than 5 years. This could be explained by the fact that type 2 diabetes is often detected late with already advanced chronic complications of the disease.

The most common non-diabetic renal diseases in patients with diabetes are IgA nephropathy (9, 4), membranous glomerulonephritis (15), or focal segmental glomerulosclerosis (3), but other non-diabetic renal diseases–tubulointerstitial diseases (11) and crescentic glomerulonephritis (13) were also listed. A different percentage of non-diabetic renal disease has been described: 7.8% in the study by Zhuo et al. (12) 12.3% in the study by Prakash et al. (10), even > 60% in several studies (2, 3, 14-16) . The incidence of non-diabetic renal disease depends on the duration of the disease before the kidney biopsy (longer duration, greater chance of developing diabetic nephropathy), as well as the selection of patients for biopsy (21-23). Non-diabetic renal disease (alone or combined with diabetic nephropathy) was diagnosed in 9 (53%) patients in our study by patients with type 2 diabetes who underwent a biopsy. Although the number of patients with diabetes whose biopsy is relatively small, a high percentage of patients with detected non-diabetic disease confirms the correct indication for the biopsy. In 4 (23.5%) patients in our group, the pathohistological analysis established hypertensive nephroangiosclerosis, which is higher in comparison with other authors (6, 12, 15). However, Shujun et al. (15) found that hypertensive nephroangiosclerosis was most often detected in the group with coexisting diabetic and non-diabetic nephropathy, which is the case in our investigated group. All this indicates that antihypertensive therapy in patients with diabetes is not sufficiently accepted in clinical practice, and that hypertension significantly contributes to kidney damage.

6. CONCLUSION

Our first experience by patients with type 2 diabetes who underwent kidney biopsy to a significant percentage of patients with diabetes who have non-diabetic kidney disease, which can certainly be proven only by a kidney biopsy. Immunosuppressives therapy in patients with glomerulonephritis was successful and resulted in partial or complete disease remission. This confirms that the diagnosis of non-diabetic kidney disease by kidney biopsy enables the implementation of disease specific therapy and thus significantly influences the course and outcome of the disease.

- **Declaration of patient consent:** The authors certify that they have obtained all appropriate patient consent forms.
- **Author's contribution:** Each author gave substantial contribution to the conception or design of the work and in the acquisition, analysis and interpretation of data for the work. Each author had role in drafting the work and revising it critically for important intellectual content. Each author gave final approval of the version to be published and they agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
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