Primary Glomerulonephritis in Diabetic Patients

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Abstract

BACKGROUND Primary glomerulonephritis (PGN) has a significant part in non-diabetic kidney disease (NDKD) in diabetes mellitus (DM) patients. In our study, we compared the clinical, demographic, and laboratory features of patients with biopsy-proven diabetic nephropathy (DN) and PGN with type 2 DM METHODS In our retrospective study, type 2 DM patients who underwent kidney biopsy between 2011-2019 were included. Demographic, clinical, and laboratory characteristics of DN and PGN patients were compared. RESULTS Seventy patients with a mean age of 55.7 ± 9.4 and 43 (61.4%) males were included. 38 (54.3%) of the patients had DN, and 32 (45.7%) had PGN. In the PGN, membranous GN (20, 62.5%) was most common. In DN patients, diabetes duration was longer; complications such as retinopathy, neuropathy, hypertension, coronary artery disease, heart failure were more frequent. At the time of renal biopsy, blood sugar, HbA1C, blood pressure, serum albumin, and proteinuria values were similar in 2 groups. The pathological damage findings of kidney biopsy in DN patients were more severe. In the first year after kidney biopsy decrease in eGFR was higher in DN patients, whereas eGFR did not change in PGN patients. CONCLUSION In a diabetic patient, fasting blood sugar, hbA1C, serum albumin, and proteinuria did not differ in the differential diagnosis of DN and PGN, whereas complications of DM (retinopathy, neuropathy, hypertension, coronary artery disease) were more characteristic in differentiation. Detection of PGN in a diabetic patient is crucial for the success of the treatment, according to DN.

PRIMARY GLOMERULONEPHRITIS IN DIABETIC PATIENTS

Background

Primary glomerulonephritis (PGN) has a significant part in non-diabetic kidney disease (NDKD) in diabetes mellitus (DM) patients. In our study, we compared the clinical, demographic, and laboratory features of patients with biopsy-proven diabetic nephropathy (DN) and PGN with type 2 DM

Methods

In our retrospective study, type 2 DM patients who underwent kidney biopsy between 2011-2019 were included. Demographic, clinical, and laboratory characteristics of DN and PGN patients were compared.

Results

Seventy patients with a mean age of 55.7 ± 9.4 and 43 (61.4%) males were included. 38 (54.3%) of the patients had DN, and 32 (45.7%) had PGN. In the PGN, membranous GN (20, 62.5%) was most common. In DN patients, diabetes duration was longer; complications such as retinopathy, neuropathy, hypertension, coronary artery disease, heart failure were more frequent. At the time of renal biopsy, blood sugar, HbA1C, blood pressure, serum albumin, and proteinuria values were similar in 2 groups. The pathological damage findings of kidney biopsy in DN patients were more severe. In the first year after kidney biopsy decrease in eGFR was higher in DN patients, whereas eGFR did not change in PGN patients.

Conclusion

In a diabetic patient, fasting blood sugar, hbA1C, serum albumin, and proteinuria did not differ in the differential diagnosis of DN and PGN, whereas complications of DM (retinopathy, neuropathy, hypertension, coronary artery disease) were more characteristic in differentiation. Detection of PGN in a diabetic patient is crucial for the success of the treatment, according to DN.

Keywords: Diabetes Mellitus, Diabetic Nephropathy, Glomerular disease, Primary Glomerulonephritis.

What's already known about this topic?

Diabetic nephropathy is the most common cause of renal involvement in diabetic patients. Non-diabetic kidney disease prevalence may vary depending on renal biopsy selection criteria, and its frequency shows significant variations. Primary glomerulonephritis has a significant part in NDKD in diabetes mellitus patients. The diagnosis of non-diabetic kidney disease is closely related to clinical findings, clinician opinion, and center experience. Besides, its treatment and prognosis are quite different from diabetic nephropathy

What does this article add?

Fasting blood sugar, hbA1C, serum albumin, and proteinuria did not differ in the differential diagnosis of diabetic nephropathy and primary glomerulonephritis, but diabetic complications, especially diabetic retinopathy, neuropathy, hypertension, coronary artery disease, heart failure were more characteristic in differentiation role diabetic nephropathy from primary glomerulonephritis.

Review criteria: how did you gather, select and analyze the information you considered in your review?

In our study between 2011-2019, 70 diabetic patients older than 18 years were evaluated retrospectively. There were 38 diabetic nephropathies and 32 primary glomerulonephrites. Clinical-demographic characteristics, treatment, and laboratory results of the patients were obtained from the medical records of our hospital. IBM SPSS v. 21 was used as the statistical method

Message for the clinic: what is the 'take-home' message for the clinician?

In a diabetic patient, primary glomerulonephritis detection is essential due to the successful response to treatment and renal survival, then diabetic nephropathy.

Introduction

Diabetic Nephropathy (DN) is the most common cause of renal involvement in diabetic patients. It causes renal histopathological changes such as glomerular basement membrane thickening, mesangial matrix increase, diffuse or nodular glomerulosclerosis[1]. Typically, early-stage hyperfiltration develops, followed by microalbuminuria and macroalbuminuria, with slow progressive renal dysfunction. Ultimately, it causes end-stage kidney disease (ESRD)[2]. Non-diabetic kidney disease (NDKD) prevalence may vary depending on renal biopsy selection criteria, and its frequency shows significant variations[3]. In renal biopsy samples of diabetic patients, 1/3 DN only, 1/3 NDKD, and 1/3 DN and disease have been reported[4,5]. Renal biopsy in diabetic patients is performed in suspicious cases, not routinely[6]. The diagnosis of NDKD is closely related to clinical findings, clinician opinion, and center experience. Besides, its treatment and prognosis are quite different from DN. In a diabetic patient, sudden onset proteinuria, the rapid loss of kidney function, active urinary sediment, and the short-term history of DM may be clues for additional pathologies[3,7].

Retrospective single-center study, we investigated the clinical, laboratory, and pathological differences of patients with biopsy-proven DN and PGN patients with type 2 DM.

Material and Method

In our study between 2011-2019, among the 1393 kidney biopsy samples of 80 samples belong to diabetic patients. These 70 diabetic patients older than 18 years were evaluated retrospectively. There were 38 DN, 32 PGN, and 10 DN with superimposed diseases (such as DN + hypertensive nephropathy, DN + crescentic

GN) according to kidney biopsy. Ten patients with superimposing conditions with DN were excluded from the study.

Clinical-demographic characteristics, treatment, and laboratory results of the patients were obtained from the medical records of our hospital.

Clinical-demographic characteristics; age, gender, body mass index, smoking, blood pressure, DM duration, accompanying diseases (Hypertension (HT), coronary artery disease (CAD), heart failure), diabetic microvascular complications (diabetic retinopathy (DR), diabetic neuropathy (DNP)) and drugs used (ACEI (angiotensin-converting enzyme inhibitor), ARB (Angiotensin receptor blocker), oral antidiabetic, Insulin) were evaluated.

At the time of kidney biopsy and follow up period at 6. and 12 months; biochemical parameters including fasting blood sugar, blood urea nitrogen, creatinine, total protein, albumin, AST, ALT, sodium, potassium, calcium, phosphorus, total cholesterol, HDL cholesterol, LDL cholesterol, triglyceride, complete blood count, HbA1C, proteinuria in 24-hour urine and glomerular filtration rate (eGFR) were recorded. eGFR was calculated according to CKD-EPI[8]. ADA (American Diabetes Association) criteria were used in the diagnosis of type 2 DM[9]. AHA criteria were used for heart failure[10].

The diagnosis of DR was made by fundoscopy and/or fluorescein angiography, and DNP was made by electromyogram (EMG). Patients using antihypertensive drugs or blood pressure [?] 140/90 were considered hypertensive.

Kidney biopsy and pathological evaluation

Indications for kidney biopsy in a diabetic patient were active urinary sediment such as dysmorphic erythrocyte, hematuria, erythrocyte, and leucocyte cylinders, the rapid loss of GFR, sudden onset nephrotic syndrome, severe proteinuria, diabetic retinopathy and proteinuria in the absence of other microvascular diseases. A kidney biopsy was performed with a tru-cut needle percutaneously with ultrasonography after obtaining the written consent of the patient.

Kidney biopsy samples were evaluated with light and immunofluorescence (IF). Paraffin-embedded tissues were cut at 3 μm for light microscopy evaluation and routine staining. All samples were stained with hematoxylin and eosin (H&E), Jones methenamine silver, Masson trichrome and periodic acid-schiff, crystal violet, and congo red dyes.

For direct immunofluorescence, the renal tissues were quickly frozen in liquid nitrogen and cut into 3 μm sections. In biopsy samples, antibodies against IgG, IgA, IgM, C3, C4, C1q, fibrinogen, kappa, and lambda were examined. All biopsy samples contained at least ten glomeruli. Glomerular basement membrane (GBM) thickening, mesangial expansion, nodular glomerulosclerosis, arteriolar hyalinosis, and arteriosclerosis were evaluated in renal biopsy specimens for the diagnosis of DN[1]. Specific histopathological diagnostic criteria were used in kidney biopsy of patients with PGN[11]. Electron microscopy was used for differential diagnosis only in suspected cases.

Chronic damage in the renal parenchyma was evaluated with interstitial fibrosis and tubular atrophy. Renal parenchymal interstitial fibrosis was expressed as a percent and tubular atrophy as yes/no. All biopsy samples were evaluated by experienced nephropathologist.

Ethical Approval All procedures performed in the study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The ethics committee has approved this study at our university.

Statistical analysis

IBM SPSS v. 21 (Chicago, IL, USA) was used as the statistical method. Continuous data were expressed as means ± SD or median. Categorical variables are given as a number (percentage) of patients. The differences

between the groups were compared using the chi-square test, Fisher-exact test, Student t-test, and Mann-Whitney U test. Differences in eGFR among the two groups over time were analyzed using repeated-measures ANOVA. Sphericity was determined by the Mauchly's analysis when the p-value > 0.05. When the Mauchly's analysis did not identify sphericity, we used repeated-measures ANOVA with Greenhouse-Geisser correction. All statistical tests used the software SPSS version 22.0 (IBM Corp., Armonk, NY, USA). The significance value was accepted as $p < 0.05$.

Results

In our study, the renal biopsy samples of 70 patients with DM type 2 were evaluated. The mean age was 55.7 ± 9.4 of patients 43 (61.4) was male. The pathologic diagnosis of kidney biopsy was 38 (54.3%) DN and 32 (45.7%) PGN. The average time of DM diagnosis at the time of kidney biopsy was 9.15 ± 7.5 years. During the biopsy, two patients were diagnosed with new DM**.** In PGN group, membranous GN (20, 62.5%), focal segmental glomerulosclerosis (FSGS) (8, 25%) IgA nephropathy (IgAN) (2, 6.3%) and minimal change disease (MDH) (2, 6.3%) were detected (Table 1).

According to PGN in DN patients; the duration of DM was longer (p<0.001), the frequencies of retinopathy (p<0.001), neuropathy(p<0.001), hypertension (p=0.0025), coronary artery disease (p=0.008), heart failure (p=0.013) were higher. In DN group hemoglobin level was lower and the number of patients with eGFR <30, <60 and <90 ml/min /1.73 m2 were higher (for all p <0.001) (Table 2).

At the time of renal biopsy, fasting blood sugar, HbA1C, blood pressure, serum albumin, and proteinuria values were similar in 2 groups. DN patients had lower eGFR values at baseline, sixth and 12th months, and higher proteinuria at sixth and 12th months than PGN patients. In the first year after kidney biopsy decrease in eGFR was higher in DN patients, whereas eGFR did not change in PGN patients. At the time of biopsy, daily proteinuria was not different between the two groups, but in the 6th and 12th months, the daily proteinuria was lower in the PGN group.

The pathological damage findings of kidney biopsy (percentage of interstitial fibrosis, presence of tubular atrophy, sclerosis glomeruli number) in DN patients were more severe.

There were differences for eGFR change between the DN group and PGN group at 0, 6, and 12th months**.** ($F(1,56)=46.336$, $p<0.001$)(Table 3 ve Figure 1). There were differences between for eGFR values each other baseline, 6th, and 12th months in DN patients ($F(1.2, 32.392)=16.727$, $p<0.001$). In PGN patients, there was no difference between eGFR changes at 0, 6, and 12th months. ($F(1.247, 7.480)=0.887$, $p=0.401$). There was no difference between eGFR changes at 0, 6, and 12 months in all patients (DN + PGN). ($F(1.304, 74.356)=2.388$, $p=0.118$)

Discussion

In our study, we found the frequency of PGN in 45.7% of 80 diabetic patients. The frequency of NDKD has been reported between 13-82.9%[3]. Membranous GN was determined most common (20, 62.5%) among diabetic patients with PGN. This result showed that diabetic patients, especially membranous GN, may play a role in renal injury.

In previous studies, IgAN has been reported to be the most common GN[7,12,13]. However, membranous GN or other GNs have been reported to be more frequent[14-19]. Since kidney biopsy selection criteria vary according to clinician and center, it is difficult to determine the frequency and cause of NDKD. Many different types of GN can be seen in diabetic patients, such as membranous GN, IgAN, and FSGS.

DR, one of the DM microvascular complications, was detected in 73.6% of our DN patients, but not in PGN patients. The prevalence of DR in patients with NDKD was reported as 13.6% and 27.2%, respectively, in the previous two studies [20,21]. As found in our study, the absence of DR can be a predictor of NDKD[20,22]. However, NDKD can be found with DR[23,24]. Kidney biopsy should be considered in the presence of an atypical scenario, even if a patient with DM has DR.

The median duration of DM was 11.5 years in DN patients and three years in PGN patients. The duration of DM is closely related to DN. The frequency of microalbuminuria and macroalbuminuria increases after ten years in type 1 DM[25]. In type 2 DM, the onset of the disease is difficult to detect, so it is recommended to investigate for DN at the time of diagnosis[26]. As in our study, the incidence of NDKD increased in patients with short diabetes duration[27-29].

Initial serum albumin, proteinuria, fasting blood sugar, and HbA1C values were not different in DN and PGN patients. In PGN patients, proteinuria decreased in the 6th and 12th months with appropriate immunosuppressive therapy, but not in the 12th month in the DN patients.

In our study, as previously reported studies, initial proteinuria[28,30] serum albumin[19,31,32] serum glucose[33], HbA1C[28,32,34] were not different in DN and NDKD patients. Similar to Liu et al.[34], our DN patients had lower serum hemoglobin levels. This result may be due to our patients with advanced CKD with DN. In our study, similar to previous studies, the mean blood pressure measurements in the two groups were not different[21,35].

Median eGFR was lower in our DN group at baseline, sixth and 12th months. In addition, DN patients had more evidence of chronic renal damage on kidney biopsy. The median eGFR value decreased at 12 months in DN but did not change in PGN patients. In other words, 1-year renal survival was higher in PGN patients than in the DN group. In previous studies, 5-year renal survival was reported to be better in the NDKD group[5,30]. In this result, the progressive natural course of DN and the successful treatment of PGN patients with appropriate immunosuppressors may play a role.

There were some limitations in our study. These are single-center, retrospective, and insufficient numbers of patients. It is the absence of a standard and exact criteria in the indication of kidney biopsy and consists of biopsy results based on our experience.

As a result, fasting blood sugar, hbA1C, serum albumin, and proteinuria did not differ in the differential diagnosis of DN and PGN, but diabetic complications, especially DR, neuropathy, hypertension, coronary artery disease, heart failure were more characteristic in differentiation role DN from PGN. It can be thought that the frequency of PGN in DM was as much as 45 %, and the clinical course was better in patients with PGN so that the biopsy indication may be similar to that of non-diabetic patients. In a diabetic patient, PGN detection is essential due to the successful response to treatment and renal survival, then DN.

Disclosure Statement

There are no potential conflicts of interest relevant to this article.

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Author Contributions

Study conception and design: Kaya B, Paydas S, Balal M.

Acquisition of data: all authors

Analysis and interpretation of data: Kaya B, Paydas S, Balal M.

Drafting of the manuscript: Kaya B, Paydas S.

Critical revision: all authors

Kidney biopsies were evaluation: Erdogan KE, Gonlusen G.

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TABLES

Table 1 : Clinical and demographic characteristics of patients (n=70)

Parameters	**Mean +SD, n(%)**
Age, years	55.7±9.4 (26-77)
Gender, M/F Diagnosis of DM at biopsy time	43/27 (61.4%/38,6%) 2(%2.8)
BMI, kg/m^2	28.1±4.2 (19.5-39.2)
Smoking	22 (%31.4)
SBP, mmHg	131.8±16.6(100-170)
DBP, mmHg	78.4±9.8 (60-100)
DM duration, year	9.15 ±7.5 (0-30)
HT	58 (%82.9)
CAD	17 (%24.3)
Retinopathy Neuropathy Hyperlipidemia Heart failure	28 (%40) 23 (%32.9) 15 (%21.4) 7 (%10)

Parameters	**Mean +SD, n(%)**
Oral anti-diabetic Insulin ACEI/ARB	33 (%47.1) 37 (%52.9) 42 (%60)
Primary GN DN Membranous GN FSGS IgA Nephropathy MCD	32 (%45.7) 38 (%54.3) 20 (%62.5) 8 (%25) 2(%6.3) 2(%

DN: Diabetic Nephropathy, GN: Glomerulonephritis, SBP: Systolic Blood pressure, DBP: Diastolic Blood pressure, HT: Hypertension, CAD: Coronary artery disease, FSGS: Focal segmental glomerulosclerosis, MCD: Minimal Change Disease, eGFR: Estimated glomerular filtration rate, ACEI: Angiotensin-converting enzyme inhibitory, ARB: Angiotensin receptor blocker

Table 2: Comparison of clinical characteristics diabetic nephropathy and primary glomerulonephritis patients

Parameter	**Diabetic Nephropathy n=38 median(mean-max) or mean+ SD**	**Primary GN n=32 median(mean-max) or mean+ SD**	p
Male/Female	22/16	21/11	0.624[3]
Age, year	55.8±9.9	55.5±9.1	0.910[1]
BMI, kg/m^2	28.1±4.1	28.1±4.3	0.967[1]
SBP, mmHg	130 (100-170)	125 (110-170)	0.183[2]
DBP, mmHg	80 (60-100)	77.5 (60-100)	0.075[2]
ACEI/ARB	21/17	21/11	0.378[3]
DM duration, year	11.5(1-30)	3(0-25)	<0.001[2]
Retinopathy, y/n	28/10	0/32	<0.001[3]
Neuropathy, y/n	22/16	1/31	<0.001[3]
CAD, y/n	14/24	3/29	0.008[3]
Heart Failure, y/n	7/31	0/32	0.013[4]
HT, y/n	35/3	23/9	0.025[3]
Insulin, y/n	26/12	11/21	0.004[3]
eGFR<90 ml/min/1.73m^2, y/n	33/5	17/15	<0.002[3]
eGFR<60 ml/min/1.73m^2, y/n	29/9	9/23	<0.001[3]
eGFR<30 ml/min/1.73m^2, y/n	18/20	2/30	<0.001[3]
eGFR_0th month, ml/min/1.73m^2	37.5(10-116)	88.5(11-127)	<0.001[2]
eGFR_6th month, ml/min/1.73m^2	23.5(8-108)	90.5 (14-132)	<0.001[2]
eGFR_12th month,ml/min/1.73m^2	15 (6-105)	89.5(15-141)	<0.001[2]
Creatinine, mg/dl	2.02 (0.62-4.63)	0.92(0.41-5.14)	<0.001[2]
Hb, gr/dl	10.8±1.87	13.3±2.0	<0.001[1]
Glucose, mg/dl	152 (60-427)	135(89-290)	0.150[2]
HbA1C, %	7.5 (5.5-13.7)	6.9 (5.5-11)	0.099[2]
T.protein, gr/dl	5.69±0.93	5.00±1.21	0.011[1]
Albumin, gr/dl	2.62±0.63	2.44±1.04	0.408[1]
Proteinuria_0. month mg/d	9841±6052	8778±4804	0.425[1]
Proteinuria_6. month, mg/d	6662(874-19467)	3350 (207-13221)	0.003[2]

Parameter	Diabetic Nephropathy n=38 median(mean-max) or mean+ SD	Primary GN n=32 median(mean-max) or mean+ SD	p
Proteinuria_12. month, mg/d	10663(750-20500)	1342(102-11575)	<0.001[2]
Proteinuria >10 gr/d, y/n	19/19	13/19	0.433[3]
Na, mmol/l	136.4±3.1	137.9±3.8	0.061[1]
Ca, mg/dl	8.39±0.68	8.49±0.78	0.563[1]
T. Cholesterol, mg/dl	249±89	289±82	0.058[1]
Triglycerides, mg/dl	203(58-665)	229(91-662)	0.308[2]
LDL, mg/dl	162±71	191±70	0.088[1]
Kidney biopsy Sclerosis glomeruli count Interstitial fibrosis,% Basal membrane thickening Mesangial matrix increase Tubular atrophy	3 (0-16) 10(0-50) 37/1 34/4 36/2	1 (0-7) 3 (0-20) 23/9 13/19 20/12	0.001[2] <0.001[2] 0.004[3] <0.001[3] 0.001[3]

[1]Student T-test, [2]Mann-Whitney U test, [3]Chi-square, [4] Fisher's exact test.

SBP: Systolic Blood pressure, DBP: Diastolic Blood pressure, DM: Diabetes Mellitus, CAD: Coronary artery disease, HT: Hypertension, DM: Diabetes Mellitus, ACEI: Angiotensin-converting enzyme inhibitory, ARB: Angiotensin receptor blocker, eGFR: estimated glomerular filtration rate

Table 3: Post-biopsy 1-year eGFR change in type 2 diabetic patients

	eGFR basal	eGFR 6th month	eGFR 12th month	p
Diabetic nephropathy	43.8±30.9	34.07±27.2	28.3±27.6	<0.001[1,b],0.006[a], 0.001[c]
Primary Glomerulonephritis	82.2±30.4	86.5±28.1	87.6±30.8	0,401
All group	63.7±36.07	61.2±38.1	58.9±41.7	0.118

Two-way repeated measured ANOVA test.

[1]Inter groups, [a]GFR basal and GFR 6th month, [b]GFR basal and GFR 12th month,[c] GFR 6th month and GFR 12th month

eGFR: estimated glomerular filtration rate