

Original Article

Non-Diabetic Renal Disease in Type 2 Diabetic Patients with Nephropathy

Jubaida Khanam Chowdhury¹, A.K.M. Rashed-ul-Hasan², Rajee Mahmud Talukder³,
Md. Nizamuddin Chowdhury⁴, Md. Nazrul Islam⁵

Received: 11 September 2019 Accepted: 30 April 2020

doi: <https://doi.org/10.3329/jemc.v10i2.53531>

Abstract

Background: In diabetic patients a good proportion of nephropathy is due to nephropathy other than diabetic renal disease. The detection of superimposed primary nondiabetic renal disease in diabetic patients has an obvious prognostic and therapeutic importance. **Objectives:** To find out the proportion of diabetic subjects suffering from nondiabetic renal disease (NDRD) and to describe histological varieties in appropriate group. **Materials and Methods:** This cross-sectional study was done in Department of Nephrology, Dhaka Medical College & Hospital, Dhaka from August 2015 to October 2016. Total 37 type 2 diabetic patients were selected. Renal biopsy was done and four cases were excluded due to inadequate sample. Tissue was sent for histopathology and direct immunofluorescence (DIF) examination. On the basis of histological diagnosis of biopsy reports patients were divided into three groups. Group I: Isolated NDRD, Group II: NDRD superimposed on diabetic nephropathy (mixed lesion) and Group III: Isolated diabetic nephropathy (DN). Each patient was evaluated for retinopathy from Ophthalmology department. Based on the presence or absence of retinopathy 33 patients were again divided into two groups. Group A includes patients with diabetic retinopathy (DR) and Group B includes patients without diabetic retinopathy. **Results:** NDRD was found in 57.6% cases, NDRD plus diabetic nephropathy (DN) in 21.2% and isolated DN in 21.2% cases. In Group A (patients with DR) NDRD, DN and mixed lesion were present in 7 (41.2%), 5 (29.4%) and 5 (29.4%) cases. In Group B (patients without DR) NDRD, DN and mixed lesion were present in 12 (75%), 2 (12.5%) and 2 (12.5%) cases respectively. *p* value (0.189) was not significant. **Conclusion:** Kidney disease other than diabetic nephropathy can occur in type 2 diabetic patients. In this study NDRD was found in high frequency. Lack of retinopathy is a poor predictor of nondiabetic kidney disease. Therefore, renal biopsy should be recommended in type 2 diabetic patients with risk factors of NDRD for accurate diagnosis, prompt initiation of disease-specific treatment and ultimately better renal outcome.

Key words: Nondiabetic renal disease; Diabetic retinopathy; Rapidly progressive renal failure; Unexplained AKI; Renal biopsy

J Enam Med Col 2020; 10(2): 73–78

1. Assistant Professor, Department of Nephrology, Enam Medical College & Hospital, Savar, Dhaka
2. Classified Eye Specialist, Combined Military Hospital, Savar Cantonment, Dhaka
3. Assistant Professor, Department of Medicine, Shaheed Monsur Ali Medical College, Uttara, Dhaka
4. Professor, Department of Nephrology, Dhaka Medical College & Hospital, Dhaka
5. Associate Professor, Department of Nephrology, Dhaka Medical College & Hospital, Dhaka

Correspondence Jubaida Khanam Chowdhury, Email: drtuli_111@ymail.com

Introduction

Diabetes mellitus (DM) represents one of the most important health problems worldwide. Over the last years, the global prevalence of type 2 diabetes mellitus (T2DM) has reached epidemic proportions fuelled by the global rise in the prevalence of obesity and unhealthy lifestyles. The natural history of the renal involvement in diabetes is better characterized in patients with type 1 diabetes mellitus (T1DM) since the beginning of diabetes is precisely known, but the natural history of diabetic nephropathy is less well-established in type 2 DM because alterations of glucose metabolism are indolent and the diagnosis of diabetes is usually established many years afterwards. A significant part of nephrology practice today consists of diabetic kidney disease (DKD).¹

Diabetic nephropathy is not the sole renal disease in diabetic patients. Nephropathy in a patient suffering from DM may not be related directly to diabetic disease. Nondiabetic renal disorder (NDRD) and other diabetic renal diseases may be present in the same patient.²

Kidney disease other than diabetic nephropathy can occur in type 2 diabetic patients and such kidney diseases are known as non-diabetic renal diseases, either isolated or superimposed on diabetic nephropathy (DN).³ The majority of diabetic patients with renal involvement are not biopsied. Patients with T2DM selected for renal biopsy are typically those with a presentation that is out of keeping with 'classical' DN. These indications can be grouped broadly into either acute presentations, with a rapid loss of renal function over a short period [acute kidney injury (AKI)] or non-acute presentations in which there are atypical clinical features. Therefore, the correct diagnosis of such patients would be crucial for disease specific therapy.⁴

DN is hard to reverse. However, certain NDRDs, such as membranous nephropathy, mesangial proliferative glomerulonephritis, IgA nephropathy are often treatable, even remittable.^{5,6} Correct diagnosis is important for the patient since prognosis and treatment may vary according to the underlying cause. Biopsy proven DN has been reported to occur in proteinuric

type 2 diabetic patients in the absence of retinopathy (RP). It means that absence of retinopathy cannot exclude the presence of DN because 50–70% patients with DN do not have retinopathy. Clearly DN can occur in absence of RP in type 2 proteinuric diabetic patients.

The presence of retinopathy suggests the occurrence of DN but does not exclude nondiabetic nephropathy. The renal-retinal relationship in type 2 diabetic patient may not be helpful for clinical diagnosis of DN and lack of RP is a poor predictor of nondiabetic kidney diseases. Therefore, presence or absence of diabetic retinopathy did not prove to be significant enough in excluding nondiabetic renal diseases.

Renal biopsy remains an integral part of clinical nephrology practice because the information it provides is pivotal for making a specific diagnosis, for planning patient management and for evaluating disease activity and prognosis.⁷ This study was undertaken to describe the histological pattern of nondiabetic renal disease (NDRD) in type 2 diabetic patients who underwent renal biopsy for their atypical presentation.

Materials and Methods

This cross-sectional study was conducted in Department of Nephrology, Dhaka Medical College & Hospital, Dhaka from August 2015 to October 2016. Total 37 type 2 diabetic patients were selected. An informed written consent was taken from each patient. Every patient went through detailed history taking and physical examination. A standardized questionnaire was used to collect demographic data, age at diagnosis of DM, clinical presentation and findings. Previous investigation reports were recorded where necessary. Ophthalmological examination of eye was done in every patient for evidence of diabetic retinopathy (DR) which was confirmed by an ophthalmologist.

Renal biopsy was done in all type 2 diabetic patients with following criteria:

- a) Presence of microscopic hematuria or active urinary sediment
- b) Nephrotic range proteinuria without retinopathy

- c) Rapidly progressive renal failure with previously stable kidney function
- d) Sudden onset of massive proteinuria
- e) Unexplained acute kidney injury (AKI) on the top of DN
- f) Nephrotic range proteinuria or renal impairment (serum creatinine ≥ 1.5 mg/dL) with duration of diabetes shorter than 5 years)
- g) Sign symptoms suggestive of multisystem disorder

Renal biopsy was not done in the following patients:

- a) Known NDRD existence by histological finding
- b) Bilateral contracted kidney
- c) Any contraindication of renal biopsy
 - a. Uncorrectable bleeding tendency
 - b. Suspected renal malignancy
 - c. Uncontrolled hypertension
 - d. Active urinary infection
 - e. Patient who did not give consent

Renal biopsy was done in total 37 patients. Four cases were excluded due to inadequate sample of renal biopsy. Kidney biopsy was done under USG guidance. Biopsy sample was analyzed by light microscopy

and immuno-fluorescence. Thirty three patients were divided into three groups on the basis of histological diagnosis of biopsy reports. Group I: Isolated NDRD, Group II: NDRD superimposed on DN (mixed lesion) and Group III: Isolated DN. Based on the presence or absence of retinopathy 33 patients were again divided into two groups: Group A – with DR and Group B – without DR.

Results

In this study renal biopsy were done in 37 cases. Among them NDRD were found in 19 (57.6%) cases, NDRD plus DN in 7 (21.2%) cases and isolated DN in 7 (21.2%) subjects. Table I shows distribution of patients according to baseline characteristics. Mean age at biopsy was nearly similar in Group I and Group II patients but it was less in Group III. Hypertension was more in Group II patients compared to other two Groups. Duration of diabetes was significantly less in the isolated NDRD group compared with the other groups. Most of the Group I patients (63.2%) had history of DM for less than 5 years, 57.1% Group II patients had history of DM for 5–10 years and 57.1% Group III patients had history of DM for >10 years. p value was significant (0.038).

Table I: Distribution of patients according to baseline characteristics (N=33)

Parameters	Group I (NDRD) (n=19)	Group II (NDRD+DN) (n=7)	Group III (DN) (n=7)	p values
Age at biopsy (years)	48.21 ± 9.45	49.29 ± 7.39	44.00 ± 12.88	0.554
	N (%)	N (%)	N (%)	
Hypertension	15 (78.9)	7 (100.0)	6 (85.7)	0.932
Duration of DM (years)				
0–5	12 (63.2)	1 (14.3)	1 (14.3)	0.038
5–10	4 (21)	4 (57.1)	2 (28.6)	
>10	3 (15.8)	2 (28.6)	4 (57.1)	

ANOVA test, Chi-square test and Fisher exact test were done to measure the level of significance.

Table II shows histological diagnosis of NDRD, NDRD plus DN and DN groups. Among the 19 biopsies of NDRD membranous glomerulonephritis was found in 5 (26.2%) cases and mesangial proliferative glomerulonephritis was found in 5 (26.2%) cases. Among the NDRD plus DN IgM nephropathy was found in 2 biopsies (28.6%) and membranoproliferative glomerulonephritis was found in 2 biopsies (28.6%). In DN group diabetes glomerulosclerosis was found in 57.2% patients.

Table II: Distributions of subjects according to histological diagnosis (N=33)

Histology	Group I (NDRD) (n=19) Number (%)	Group II (NDRD+DN) (n=7) Number (%)	Group III (DN) (n=7) Number (%)
Membranous glomerulonephritis	5 (26.2)		
Chronicsclerosing glomerulonephritis	3 (15.7)		
C3 glomerulopathy	1 (5.2)	1 (14.3))	
Mesangial proliferative glomerulonephritis	5 (26.2)	1 (14.3)	
IgM nephropathy		2 (28.6)	
Focal segmental glomerulosclerosis	1 (5.2)		
Membranoproliferative glomerulonephritis	1 (5.2)	2 (28.6)	
Lupus nephritis, class –III	1 (5.2)		
Crystal-induced nephropathy	1 (5.2)		
IgA nephropathy	1 (5.2)		
Crescentic glomerulonephritis		1 (14.3)	
Diabetic nephropathy class III (Kimmelstiel-wilson lesion)			2 (28.6)
Diabetic nephropathy, class- IV			1 (14.3)
Diabetic glomerulosclerosis			4 (57.2)

Table III shows distribution of patients according to ophthalmoscopic findings. In Group A (patients with DR) NDRD, DN and mixed lesion were present in 7 (41.2%), 5 (29.4%) and 5 (29.4%) cases. In Group B (patients without DR) NDRD, DN and mixed lesion were present in 12 (75%), 2 (12.5%) and 2 (12.5%) cases respectively. p value (0.189) was not significant.

Table III: Distribution of patients according to ophthalmoscopic findings (N= 33)

Pattern of nephropathy	Group A Number (%)	Group B Number (%)	p value
NDRD	7 (41.2)	12 (75.0)	0.189
DN	5 (29.4)	2 (12.5)	
Mixed lesion (NDRD+DN)	5 (29.4)	2 (12.5)	

Fisher exact test was done to measure the level of significance.

Table IV shows biochemical parameters of different groups of patients. Serum creatinine levels were significantly higher in patients with DN (isolated as well as with superimposed disease) compared with those with NDRD, but p value was not significant ($p > 0.654$). Nephrotic range proteinuria was more in NDRD plus DN compared to NDRD and DN, and p value (0.054) was not significant. Microscopic hematuria was more in NDRD group patients (79%) than in other two groups.

Table IV: Distributions of subjects according to biochemical parameters (N=33)

Parameters	Group I (NDRD) (n=19)	Group II (NDRD +DN) (n=7)	Group III (DN) (n=7)	p-value
S. creatinine (mg/dL)	2.82 ± 2.63	3.81 ± 1.98	3.04 ± 2.15	0.654
S. albumin (gm/dL)	2.39 ± 0.60	2.35 ± 0.23	2.62 ± 0.28	0.511
Proteinuria (gm/dL)	7.91 ± 6.01	12.01 ± 4.67	5.07 ± 1.72	0.054
HbA1c (%)	7.49 ± 1.74	9.27 ± 1.19	7.68 ± 2.53	0.054
Microscopic hematuria (%)	15 (79%)	5 (71%)	4 (57%)	0.900
Serum total cholesterol (mg/dL)	270.5 ± 101.1	215.8 ± 55.4	215.8 ± 55.4	0.289

Discussion

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.⁸⁻¹⁰

DN is one of the most frequent and clinically important complications of diabetes mellitus. It affects approximately 40% of the patients who have diabetes for more than 20 years and has become the leading cause of end stage renal disease (ESRD) worldwide.^{11,12}

In this study it was observed that mean age (years) at biopsy was nearly similar in Group I (Isolated NDRD) and Group II (NDRD superimposed on DN), 48.21 ± 9.45 and 49.29 ± 7.39 years respectively, but in Group III (Isolated DN) mean age was 44 ± 12.88 years which was lower than in other two groups. Unnikrishnan et al¹³ covering South Indian population reported the average age of patients as 51 ± 12 years. Mak et al¹⁴ reported average age was 57 ± 1.8 years in patients having DN and 50 ± 1.9 years in patients having mixed lesions.

The presence of microscopic hematuria has been suggested by different authors to be one of the atypical features indicating presence of NDRD. In the present study it was found that microscopic hematuria was more in NDRD group patients (79%) than in other two groups which was consistent with the findings in the studies done by Mak et al¹⁴ and Matias et al¹⁵. Microscopic hematuria in DN patients is glomerular

hematuria. The most likely mechanism could involve pathological changes in the glomerular basement membrane and ruptured pseudoaneurysms.

In this study isolated DN was in 21.2%, pure NDRD in 57.6% and mixed lesions in remaining 21.2% cases. Prakash et al¹⁶ found isolated DN in 38.7% cases, pure NDRD in 41.9% and mixed lesions in remaining 19.4% cases. Idiopathic membranous nephropathy was the most common NDRD lesion noted in 21% cases but in our study it was 26.2%. Castellano et al¹⁷ reported DN in 45% cases, and NDRD in 55% patients and membranous nephropathy was the commonest NDRD lesion.

In the present study among the superimposed (DN plus NDRD) lesion IgM nephropathy and membranoproliferative GN was found in 2 (28.6%) out of 7 biopsies whereas among DN diabetes glomerulosclerosis was most frequent (57.2%).

Duration of diabetes was significantly less in the isolated NDRD group compared with the other groups. Thus, shorter duration of diabetes and older age could be risk factors for NDRD. Lee et al¹⁸ also concluded that a shorter duration of diabetes was significantly associated with NDRD. Similar results were reported by Tone et al¹⁹ and Huang et al²⁰.

Absence of diabetic retinopathy is said to be one of the important predictors of NDRD. In people with type 1 diabetes, the association is stronger than in those with type 2 diabetes. This correlation has been reported by Lee et al¹⁸ who showed that absence of retinopathy was one of the significant factors that

predicts NDRD. Tone et al¹⁹ reported that absence of retinopathy showed the highest sensitivity (87%) and specificity (93%) for the prediction of NDRD. In our study patients without DR, NDRD, DN and mixed lesion were found in 12 (75%), 2 (12.5%) and 2 (12.5%) cases respectively.

In patients with short duration of DM, heavy proteinuria, active urinary sediment or rapid deterioration of renal function renal biopsy showed NDRD in 57.6% cases, DN in 21.2% and mixed lesion in 21.2% cases. Therefore, renal biopsy should be recommended in type 2 diabetic patients with risk factors of NDRD for accurate diagnosis, prompt initiation of disease-specific treatment and ultimately better renal outcome.

References

1. Stanton RC. Clinical challenges in diagnosis and management of diabetic kidney disease. *American Journal of Kidney Disease* 2014; 63: S3–21.
2. Olsen S. Identification of non-diabetic glomerular disease in renal biopsies from diabetics—a dilemma. *Nephrology Dialysis Transplant* 1999; 14(8): 1846–1849.
3. Prakash J, Lodha M, Singh SK, Vohra R, Raja R, Usha. Diabetic retinopathy is a poor predictor of type of nephropathy in proteinuric type 2 diabetic patients. *J Assoc Physician India* 2007; 55: 412–416.
4. Gonzalez Suarez ML, Thomas DB, Barisoni L, Fornoni A. Diabetic nephropathy: is it time yet for routine kidney biopsy? *World J Diabetes* 2013; 4: 245–255.
5. Mak SK, Gwi E, Chan KW, Wong PN, Lo KY, Lee KF et al. Clinical predictor of non-diabetic renal disease in patients with non-insulin dependent diabetes mellitus. *Nephrol Dial Transplant* 1997; 12: 2588–2591.
6. Pham TT, Sim JJ, Kujubu DA, Liu IL, Kumar VA. Prevalence of nondiabetic renal disease in diabetic patients. *Am J Nephrol* 2007; 27: 322–328.
7. Korbet SM. Percutaneous renal biopsy. *Semin Nephrol* 2002; 22: 254–267.
8. Chang TI, Park JT, Kim JK, Kim SJ, Oh HJ, Yoo DE et al. Renal outcomes in patients with type 2 diabetes with or without coexisting non-diabetic renal disease. *Diabetes Res Clin Pract* 2011; 92: 198–204.
9. Soleymanian T, Hamid G, Arefi M, Najafi I, Ganji MR, Amini M et al. Non-diabetic renal disease with or without diabetic nephropathy in type 2 diabetes. Clinical predictors and outcome. *Ren Fai* 2015; 37: 572–575.
10. Li L, Zhang X, Li Z, Zhang R, Guo R, Yin Q et al. Renal pathological implications in type 2 diabetes mellitus patients with renal involvement. *J Diabetes Complications* 2017; 31: 114–121.
11. Kramer H, Molitch ME. Screening for kidney disease in adults with diabetes. *Diabetes Care* 2005; 28: 1813–1816.
12. Gross JL, de Azevedo MJ, Silveiro SP, Canani LH, Caramori ML, Zelmanovitz T. Diabetic nephropathy: diagnosis, prevention, and treatment. *Diabetes Care* 2005; 28: 164–176.
13. Unnikrishnan RI, Rema M, Pradeep R, Deepa M, Shanthirani CS, Deepa R et al. Prevalence and risk factor of diabetic nephropathy in an urban south Indian population. The Chennai Urban Rural Epidemiology study (CURES45). *Diabetes Care* 2007; 30: 2019–2024.
14. Mak SK, Gwi E, Chan KW, Wong N, Lo Y, Lee F et al. Clinical predictors of non-diabetic renal disease in patients with non-insulin dependent diabetes mellitus. *Nephrol Dial Transplant* 1997; 12: 2588–2591.
15. Matias P, Viana H, Carvalho F, Santos JR. Diabetes mellitus and renal disease: when to perform a renal biopsy? *Port J Nephrol Hypert* 2009; 23: 167–173.
16. Prakash J, Gupta T, Prakash S, Bhushan P, Usha, Sivasankar M et al. Non-diabetic renal disease in type 2 diabetes mellitus: Study of renal-retinal relationship. *Indian J Nephrol* 2015; 25: 222–228.
17. Castellano I, Covarsí A, Novillo R, GomezMartino JR, Ferrando L. Renal histological lesions in patients with type II diabetes mellitus. *Nefrologia* 2002; 22: 162–169.
18. Lee EY, Chung CH, Choi SO. Non-diabetic renal disease in patients with non-insulin dependent diabetes mellitus. *Yonsei Med J* 1999; 40: 321–326.
19. Tone A, Shikata K, Matsuda M, Usui H, Okada S, Ogawa D et al. Clinical features of non-diabetic renal diseases in patients with type 2 diabetes. *Diabetes Res Clin Pract* 2005; 69: 237–242.
20. Huang F, Yang Q, Chen L, Tang S, Liu W, Yu X. Renal pathological change in patients with type 2 diabetes is not always diabetic nephropathy: a report of 52 cases. *Clin Nephrol* 2007; 67: 293–297.