Original Research

Evaluation of Non-Diabetic Kidney Diseases in Patients with Type 2 Diabetes Mellitus: An Institutional Based Study

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Abstract
Background: In individuals with type 2 diabetes mellitus (DM), nondiabetic renal disease (NDRD) is recognized as a contributing factor to proteinuria and renal failure. Hence, this study was conducted to analysenon-diabetic kidney disease in patients with type 2 diabetes mellitus.
Materials & Methods: Data of a total of 200 subjects was screened among which ultrasound-guided kidney biopsies were performed. Out of these 200 subjects, 8 subjects were found to be affected with type 2 diabetes mellitus. An automatic biopsy instrument was used for obtaining renal biopsies. The process was ultrasound-guidedand lower pole of the left kidney was punctured. Immunofluorescence assessment of the biopsy specimens was done. Complete demographic and clinical details of all the patients were obtained. Thorough medical examination of all the patients was done. Blood samples were also obtained, and hemodynamic profile was evaluated. All the results were recorded on a Microsoft excel sheet.
Results: Out of 200 patients screened, type 2 diabetes mellitus was found to be present in 8 patients. The majority of the patients showed nephrotic syndrome as the main indication of renal biopsy. On analyzing histopathologic specimen of these 8 patients, final diagnosis of most of the patients was diabetic nephropathy while Lupus nephritis + diabetic nephropathy was the diagnosis in one patient.
Conclusion: Kidney biopsy played a crucial role in identifying non-diabetic renal disease in patients with clinical suspicions.
Keywords: Type 2 Diabetes Mellitus, Kidney Biopsy,Non-Diabetic Kidney Disease.

INTRODUCTION

Proteinuria in diabetic patients is usually interpreted as a clinical manifestation of diabetic nephropathy (DN). However, not all diabetic subjects with proteinuria have DN. Nondiabetic renal disease (NDRD) have been seen to cause proteinuria in diabetic patients. There is a wide variation of prevalence of NDRD. The occurrence of NDRD in type 1 diabetes mellitus (DM) is rare in comparison with those with type 2DM. Although the exact incidence of NDRD is not known, frequency varies from 5% to 71% in various studies.[1] It is seen in 26.7% of Asian and 22% of European patients.[2,3] Kidney biopsy is an unbiased method but is seldom used in proteinuric diabetic patients. Olsen, in a meta-analysis of similar studies, found the frequency of glomerulonephritis (GN) to be between 0 and 66%. This variation is probably due to variable selection criteria and geographical differences.[4] Late age of onset of DM, absence of neuropathy, absence of retinopathy, and presence of other systemic diseases are reported as markers of NDRD in different studies. However, it remains unclear which clinical factors have greater value in the prediction of NDRD. As the reported incidence of NDRD in type 2 DM is high, it is necessary to predict, diagnose, and treat concurrent glomerular diseases because of the prognostic and therapeutic importance.[5]Diabetes Mellitus (DM) affects the kidney either in the form of diabetic kidney disease (DKD), non-diabetic kidney disease (NDKD), or both overlapping.[6] Despite an increasing prevalence of type-2 diabetes mellitus (T2DM), the overall prevalence of DKD remained stable.[7] Apart from better glycemic

control by early diagnosis, this could be due to the improved understanding of the pathogenesis, at least of the hemodynamic mechanisms, which led to the discovery and use of newer therapeutic agents, including renin-angiotensin-aldosterone system blockers (RAASB) and sodium-glucose transporter-2 inhibitors (SGLT2I). Recently, an increasing prevalence of NDKD in diabetics has been reported, 8 which may be due to the aging population, higher exposure to infections, increasing incidence of monoclonal gammopathies and other malignancies.[8,9]

In the last decades, diabetic nephropathy has become the leading cause of end-stage kidney disease worldwide.[10] 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.[11]

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.[12]

Hence, this study was conducted toanalysenon-diabetic kidney disease in patients with type 2 diabetes mellitus.

MATERIALS & METHODS

The present study was conducted in Department of Nephrology, Patna Medical College, Patna, Bihar (India) for evaluating non-diabetic kidney disease in patients with type 2 diabetes mellitus. Data of a total of 200 subjects was screened among which ultrasound-guided kidney biopsies were performed. Out of these 200 subjects, 12 subjects were found to be affected with type 2 diabetes mellitus. An automatic biopsy instrument was used for obtaining renal biopsies. The process was ultrasound-guidedand the lower pole of the left kidney was punctured. Immunofluorescence assessment of the biopsy specimens was done. Complete demographic and clinical details of all the patients were obtained. Thorough medical examination of all the patients was done. Blood samples were also obtained, and hemodynamic profile was evaluated. All the results were recorded on a Microsoft excel sheet. This was followed by assessment by SPSS software.

RESULTS

Out of 200 patients screened, type 2 diabetes mellitus was found to be present in 8 patients. Mean age of the patients was 53.5 years. Among these 8 patients, 5 patients were males while the remaining 3 patients were females.The mean duration of diabetes among these patients was 5 years. Mean proteinuria was 8.19 g/day.The majority of the patients showed nephrotic syndrome as the main indication of renal biopsy. On analyzing histopathologic specimen of these 8 patients, final diagnosis of most of the patients was diabetic nephropathy while Lupus nephritis + diabetic nephropathy was the diagnosis in one patient.

Table 1: Demographic data of the patients with type 2 diabetes mellitus

Patient number	Age	Gender	Duration of disease (years)	Proteinuria (g/Day)
1	49	Male	6	6.45
2	61	Male	5	10.56
3	48	Female	3	8.69
4	53	Female	5	4.74
5	51	Male	7	6.36
6	56	Male	5	13.51
7	59	Male	6	10.85
8	51	Female	3	4.38

Table 2: Indication for biopsy of the patients with type 2 diabetes mellitus

Patient number	Indication for renal biopsy	Histopathologic finding
1	**Nephrotic syndrome**	Membranous glomerulonephritis
2	**Acute onset nephrotic syndrome**	Diabetic nephropathy
3	**Nephrotic syndrome with microscopic hematuria**	Hypertensive nephroangiosclerosis
4	**Nephrotic syndrome, diabetes mellitus duration 5 years**	Diabetic nephropathy
5	**Rapidly deterioration of CKD**	Diabetic nephropathy
6	**Nephrotic syndrome, ANA+, diabetes mellitus duration < 5**	Lupus nephritis + diabetic

	years	nephropathy
7	**Nephrotic syndrome**	Inadequate sample
8	**Acute onset nephrotic syndrome**	Diabetic nephropathy

DISCUSSION

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 endstage renal failure in a large percentage. Therefore, it is very important to diagnose non-diabetic kidney disease in patients with DM, as this significantly improves the prognosis of the disease. [13] Hence, this study was conducted to analysenon-diabetic kidney disease in patients with type 2 diabetes mellitus.In the present study, out of 200 patients screened, type 2 diabetes mellitus was found to be present in 8 patients. The mean age of the patients was 53.5 years. Among these 8 patients, 5 patients were males while the remaining 3 patients were females. The mean duration of diabetes among these patients was 5 years. Mean proteinuria was 8.19 g/day.The majority of the patients showed nephrotic syndrome as the main indication of renal biopsy. On analyzing histopathologic specimen of these 8 patients, final diagnosis of most of the patients was diabetic nephropathy while Lupus nephritis + diabetic nephropathy was the diagnosis in one patient. A study by Das U et al, data of patients with type 2 DM who underwent renal biopsy in this institute from 1990 to 2008 were analyzed retrospectively. Patients were categorized as isolated NDRD, NDRD with DGS, and isolated DGS. A total of 75 patients were included. Mean age was 45 ± 10.2 years, male to female ratio was 3.1: 1, median duration of DM was 12 months (range, 1 year-15 years), proteinuria was 4.2 ± 3.4 g/day, and serum creatinine was 4.3 ± 3.9 mg/dl. Hypertension was observed in 63 (84%) cases and microscopic hematuria in 24 (32%) cases. Nephrotic syndrome (38.7%) was the commonest clinical presentation. Forty-eight (64%) cases had NDRD and 27 (36%) had DGS. The commonest NDRD was minimal change disease (12.5%). Three (6.3%) patients had lupus nephritis. Tubulointerstitial nephritis has been observed in 10.4% of patients. No significant differences between NDRD and DGS patients were found except hypertension which was significantly high in the DGS group. Acute kidney injury and nephritic syndrome were not observed in the DGS group. The incidence of biopsyproven NDRD in type 2 DM was high. Kidney biopsy aided in the detection of NDRD in clinically suspected patients.[14]Another study by Grujicic M et al, investigated 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.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.In 18 patients with type 2 DM, the average duration of the disease was 5.9 years, 5 patients had 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. An 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.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.[15] Prasad N et al, conducted observational study, prospectively collected the data of kidney biopsies of patients aged ≥ 18 years with T2DM admitted between 1 August 2005 and 31 July 2022. The clinical, demographic and histopathological data were evaluated. The spectrum of kidney involvement in the form of DKD and/or NDKD was studied. The impact of these findings with the use of drugs retarding disease progression was also analyzed. A total of 5485 biopsies were performed during the study period and of these 538 patients had T2DM. The mean age of the study population was 56.9 ± 11.5 years and 81% were males. The mean duration of DM was 6.4 ± 6.1 years. Diabetic retinopathy (DR) was noted in 29.7%. The most common indication for biopsy was an acute rise in creatinine (147, 27.3%). Amongst the 538 diabetic patients who underwent biopsy, histological features only of DKD were noted in 166 patients (33%), NDKD alone in 262 (49%) and NDKD with DKD lesions in 110 (20%). On multivariate analysis, duration of DM less than 5 years, absence of CAD, absence of DR, oliguria at presentation, an acute rise in creatinine and

low C3 were associated with NDKD. The prevalence of NDKD among diabetics and ATIN in particular might be on an increasing trend in the current era of changing T2DM epidemiological patterns. The use of anti-proteinuric agents was associated with lesser degrees of histopathological chronicity in T2DM.[16] Prakash J et al, analysed prevalence and spectrum of non-diabetic renal disease in type 2 diabetic patients.Two hundred sixty type 2 diabetic with clinical renal diseases were screened for evidence of NDRD, between April 1997 to March 1999. Renal disease other than diabetic nephropathy was found in 32 (12.3%) patients. Their (male 23; female 9) age ranged between 35-72 (mean 54.15+/-10.3) years. The duration of diabetes was < 5 years in 14 (43.7%), between 5-9 years in 8 (25%) and > 10 years in 10 (31.2%) patients.The presenting clinical syndromes were: chronic renal failure 15 (47%), acute nephritic syndrome 6 (18.7%), nephrotic syndrome 5 (15.6%), acute renal failure 4 (12.5%) and rapidly progressive glomerulonephritis (RPGN) in 2 (6.2%) cases. Overall, incidence of glomerular (46.8%) and tubulo-interstitial lesions (53.2%) were almost equal in type 2 diabetes patients. The spectrum of non-diabetic renal diseases includes: primary isolated glomerulopathy 12 (37.5%); mesangioproliferative GN superimposed on diabetic glomerulosclerosis (DGS) in 3 (9.3%); acute tubulo-interstitial nephropathy (TIN) 4 (12.5%); chronic TIN 10 (31.25%) and three patients had chronic pyelonephritis. Diabetic retinopathy was absent in 22 (69%) cases where 10 (31%) patients had background diabetic retinopathy. None of the patients with non-diabetic glomerular disease had diabetic retinopathy, except two who had DGS in addition to mesangioproliferative GN on renal biopsy. The background diabetic retinopathy was seen in 47% of patients with TIN without clinical evidence of diabetic nephropathy. The recovery of renal function or clinical improvement was observed in 47% of patients with NDRD with institution of appropriate treatment.The prevalence of NDRD was 12.3% in type 2 diabetic patients. Both non-diabetic glomerulopathy (47%) and tubulo-interstitial nephropathy (53%) can occur with nearly equal frequency in such patients. It is also gratifying to diagnose and treat NDRD in type 2 diabetics in selected cases.[17]Erdogmus S et al,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.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. The 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.[18]

CONCLUSION

Kidney biopsy played a crucial role in identifying non-diabetic renal disease in patients with clinical suspicions.

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