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Original Article

Non-Diabetic Renal Disease in Patients with Type-2 Diabetes Mellitus

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ABSTRACT. Diabetic nephropathy (DN) is the leading cause of end-stage renal disease in diabetics worldwide, yet most patients with type-2 diabetes mellitus are not formally evaluated with a renal biopsy. The diagnosis is almost always based on clinical grounds. A wide spectrum of non-diabetic renal disease (NDRD) is reported to occur in patients with type-2 diabetes. It has been estimated that up to one-third of all diabetic patients who present with proteinuria are suffering from NDRD. The aim of this analysis was to evaluate the prevalence and etiology of NDRD in patients with type-2 diabetes. We retrospectively reviewed the medical records of patients with type-2 diabetes who underwent kidney biopsy on clinical suspicion of NDRD (absence of diabetic retinopathy and/or neuropathy; short duration of diabetes, i.e. less than five years) from January 2003 through December 2007 at the Aga Khan University Hospital, Karachi. Based on the biopsy findings, patients were grouped as Group-I, isolated NDRD; Group-II, NDRD with underlying DN; and Group-III, isolated DN. Of 68 patients studied, 75% were males and the mean age was 56 years. The mean duration of diabetes was nine years. Group-I included 34 patients (52%), Group-II included 11 patients (17%) and Group-III included 23 patients (31%). Among the Group-I patients, the mean age was 56 years (41–77 years). The most common NDRDs were acute interstitial nephritis (32%), diffuse proliferative glomerulonephritis (17%); membranous nephropathy (12%) and crescentic glomerulonephritis (12%). Among Group-II, the mean age was 60 years (46–71 years), and the most common lesion was interstitial nephritis superimposed on underlying DN (63% cases). Among Group-III, the mean age was 53 years (42–80 years). The mean proteinuria was 5, 6.3 and 7.3 g/24 h of urine collection in Groups I, II and III, respectively ($P = NS$). The mean duration of diabetes was 7.3, 11.7 and 10.7 years in Groups I, II and III, respectively. The duration of diabetes was significantly less in Group-I compared with Group-II and Group-III ($P = 0.04$). Our study suggests that the prevalence of NDRD (either isolated or superimposed on underlying DN) is high in appropriate clinical settings. Performing renal biopsy in diabetics with no extrarenal end organ damage other than nephropathy helps to diagnose and treat NDRD. This is the first report from Pakistan documenting the prevalence of NDRD in patients with type-2 diabetes.

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Introduction

The incidence and prevalence of diabetes mellitus are on the rise worldwide.¹ Nearly 21 million people in the United States (7% of the population) have diabetes, and about one-third of those with diabetes are unaware of their condition.² Worldwide, 171 million people have

diabetes.² It is projected that in the US population, the prevalence of diabetes will increase by 165% between 2000 and 2050, with the greatest increase being in older individuals (>75 years) and among African Americans.³ The global burden of diabetes is expected to double between 2000 and 2030, with the greatest increase in prevalence occurring in the Middle East, Sub-Saharan Africa and India.² This is attributed to the progressive demographic transition worldwide with urbanization along with increased and prolonged exposure of the ageing population to unhealthy lifestyles, including a calorie-dense diet and physical inactivity.⁴

Diabetic nephropathy (DN), one of the complications of diabetes, has been the leading cause of end-stage renal disease (ESRD) in developed countries, and has been increasing rapidly in many developing countries.^{5,6} According to the United States Renal Dialysis Registry System (USRDS) 2006 Report, DN is the primary cause of kidney failure in approximately 45% of the patients receiving dialysis therapy.⁷ Moreover, 15–23% of the patients with diabetes are estimated to have advanced stages (moderate to severe) of chronic kidney disease.^{8,9}

But, this story is not simple because all renal diseases that occur in diabetic patients need not always be DN. It has been estimated that up to one-third of diabetic patients who present with proteinuria are suffering from non-diabetic renal diseases (NDRD).¹⁰⁻¹⁴ The usual criteria for suspecting NDRD and performing kidney biopsy in patients with type-1 diabetes are presence of microscopic hematuria, absence of diabetic retinopathy, uncharacteristic change in kidney function or presence of other systemic diseases.¹⁵ However, the validity of these clinical conditions is not well established for patients with type-2 diabetes. The occurrence of isolated NDRD or with concurrent DN has important implications for therapy and prognosis as DN is hard to reverse, but some NDRD are often treatable and even remittable.

The prevalence of NDRD in patients with type-2 diabetes has been variably reported in the published literature. Studies from India have

reported the prevalence of NDRD to vary from 12% to 72.5%.¹⁶ The prevalence and nature of NDRD in patients with type-2 diabetes is not documented in Pakistan.

The aim of this study is to assess the prevalence and to study the etiology of NDRD and correlate it with clinical parameters such as duration of diabetes, amount of proteinuria and microscopic hematuria at a tertiary care hospital in Pakistan.

Materials and Methods

We retrospectively reviewed the medical records of patients who underwent kidney biopsy from January 2003 through December 2007 at our institute, The Aga Khan University Hospital. Of 273 patients who had undergone renal biopsy, 68 had type-2 diabetes and were biopsied on clinical suspicion of NDRD.

The indications for renal biopsy in the diabetic patients included the following:

- Nephrotic range proteinuria or renal impairment (serum creatinine ≥ 1.5 mg/dL) in the absence of diabetic retinopathy
- Nephrotic range proteinuria or renal impairment (serum creatinine ≥ 1.5 mg/dL) with duration of diabetes shorter than five years
- Unexplained microscopic hematuria, defined as more than three red blood cells per high power field in a centrifuged urine sample
- Unexplained acute kidney injury, defined as unexplained rise in serum creatinine ≥ 0.5 mg/dL in a patient with previously normal kidney function
- Rapidly declining renal function in patients with previously stable renal function
- Sudden onset of nephrotic range proteinuria with normal kidney function.

Patients with ESRD were excluded. The biopsy material was processed for light microscopy and immunofluorescence. DN was diagnosed by an experienced renal pathologist by the presence of mesangial expansion and diffuse inter-capillary glomerulosclerosis, with or without the nodular Kimmelstiel–Wilson formation, basement membrane thickening, fibrin caps or capsular drops.

Based on the biopsy findings, the patients were categorized as follows:

Group-I: Isolated NDRD

Group-II: NDRD superimposed on underlying DN

Group-III: Isolated DN

Clinical details including age, gender, duration of diabetes, presence or absence of hypertension, presence or absence of diabetic retinopathy and indication for biopsy were recorded from the case records. The laboratory profile noted included blood urea nitrogen (BUN), serum creatinine, urinalysis and degree of proteinuria either by 24-h urine collection or by spot urine protein to creatinine ratio.

Definitions

The duration of diabetes was defined as the period between the age at onset and age at performing renal biopsy. Hypertension was defined as blood pressure more than 140/90 mmHg with or without antihypertensives. Diabetic retinopathy was diagnosed on fundoscopy by an ophthalmologist; diagnostic findings included presence of background retinopathy (microaneurysms, hemorrhages, soft exudates, hard exudates) with or without proliferative changes.

Statistical Analysis

Correlation of histological findings with clinical and biochemical parameters was carried out. Collected data were analyzed using SPSS for windows version 15. Data are expressed as mean \pm SD. Differences between groups were assessed by using the univariate chi-square test for categorical variables, unpaired t-test or ANOVA for continuous variables where appropriate; $P < 0.05$ was considered statistically significant.

Results

A total of 68 patients with type-2 diabetes underwent renal biopsy during the study period. Thirty-four patients (52%) belonged to Group-I (isolated NDRD), 11 (17%) to Group-II (NDRD with underlying DN) and 23 (31%) to

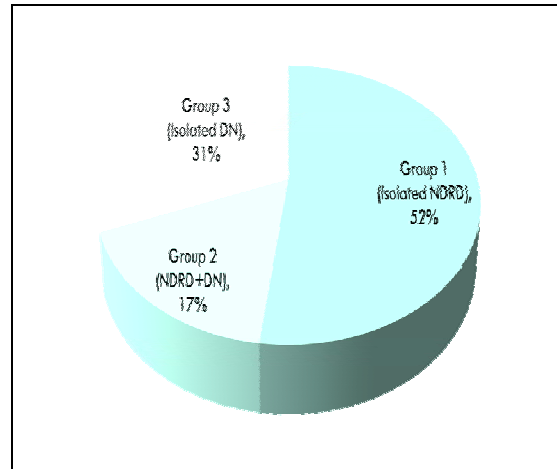


Figure 1. Group frequencies among the study patients.

Group-III (isolated DN) (Figure 1). Clinical and laboratory parameters in the three groups are shown in Table 1. Males outnumbered females in all the groups. The duration of diabetes was significantly less in Group-I than in Group-II and Group-III ($P = 0.04$). The prevalence of hypertension was similar in all three groups. Level of proteinuria was higher in Group-II and Group-III when compared with Group-I, but the difference was not statistically significant. The serum creatinine levels were significantly higher in Group-II and Group-III ($P < 0.0001$). The incidence of microscopic hematuria was not different among the three groups.

Indications for renal biopsy included rapidly declining renal function in 31 patients (45.5%), absence of diabetic retinopathy in 12 patients (17.6%), unexplained acute kidney injury in 12 patients (17.6%) and duration of diabetes mellitus less than five years in nine patients (13.2%), and miscellaneous in eight others (Table 2).

The histological lesions identified in patients in Group-I and Group-II are presented in Table 3. Among Group-I patients, the most common NDRD were acute interstitial nephritis (AIN) (32%), diffuse proliferative glomerulonephritis (20.5%); membranous nephropathy (12%) and crescentic glomerulonephritis (12%), while Group-II predominantly comprised AIN (63%).

Table 1. Clinical and laboratory parameters in the different groups of patients studied.

Parameters	Total n = 68	Group-I n = 34 (NDRD)	Group-II n = 11 (NDRD + DN)	Group-III n = 23 (DN)	P-value
Age at biopsy (years)	56 ± 8	56 ± 9	60 ± 8	53 ± 9	NS
Gender (M/F)	51/17	20/14	10/1	21/2	
Duration of diabetes (years)	9 (SD 6.8)	7.3 (SD 7)	11.7 (SD 10)	10.7 (SD 10)	0.04
Hypertension (%)	89.7	75.7	91.6	100	NS
Mean serum creatinine (mg/dL)	4.5 (SD 2.56)	3.45 (SD 1.9)	5.1 (SD 2.1)	5.4 (SD 3)	<0.0001
Proteinuria (g/24 h)		5 (0.3–20)	6.3 (2–10)	7.3 (1–13)	NS
Microhematuria (%)	51.4	60.6	41.6	34.7	NS

NDRD: non-diabetic renal disease, DN: diabetic nephropathy

Discussion

DN is one of the most frequent and clinically important complications of diabetes mellitus. It affects approximately 40% of the patients who have had diabetes for more than 20 years and has become the leading cause of ESRD worldwide.^{5,6,17}

The diagnosis of DN is almost always based on clinical grounds and is supported by a long history of diabetes, evidence of target organ damage and proteinuria preceding azotemia. However, DN is not the only renal disease in diabetes. Many NDRD have been uncovered by renal biopsy. It has been shown that renal disease in patients suffering from type-1 diabetes for more than 10 years, especially in the presence of diabetic retinopathy or neuropathy, is usually the result of DN, and it has been proven histologically in >95% of the patients.

But, this is not the case in patients with type-2

diabetes.¹⁸⁻²⁰ Kidney biopsies from patients with type-2 diabetes, with renal disease or proteinuria, show that they comprise a more heterogeneous group of renal lesions other than DN.^{10-13,16,21-28}

Different predicting factors have been identified in diabetic patients found to have NDRD, including late onset of diabetes, absence of neuropathy/retinopathy, abrupt onset or progression of renal disease (massive proteinuria or renal insufficiency) and presence of microscopic hematuria.^{27,29-31}

Among patients with type-2 diabetes who had renal biopsy, the prevalence of NDRD varies widely in the published literature, from 12% to 79%, depending on the selection criteria and the population being studied.^{10-13,16,21-28,32-34} In our study, all patients had type-2 diabetes, and 69% of the patients had NDRD (either isolated or superimposed on underlying DN).

We found a predominance of males in all three

Table 2. Indications for kidney biopsy in the study patients.

Indications	Total (n = 68) n (%)	Group-I (Isolated NDRD) (n = 34) n (%)	Group-II (NDRD + DN) (n = 11) n (%)	Group-III (Isolated DN) (n = 23) n (%)
Rapidly declining renal function in patients with previously stable renal function	31 (45.5)	10 (30.3)	8 (66.6)	13 (56.2)
Heavy proteinuria or renal impairment in the absence of diabetic retinopathy	12 (17.6)	5 (15.1)	2 (16.6)	5 (21.7)
Unexplained acute renal failure	12 (17.6)	10 (30.3)	Nil	2 (8.6)
Heavy proteinuria or renal impairment with duration of diabetes mellitus less than five years	9 (13.2)	5 (15.1)	2 (16.6)	2 (8.6)
Unexplained microscopic hematuria	3 (4.4)	3 (9.0)	Nil	Nil
Heavy proteinuria	1 (1.4)	Nil	Nil	1 (4.3)

NDRD: non-diabetic renal disease, DN: diabetic nephropathy

Table 3. Histological diagnosis in patients in Group-I and Group-II.

Histology	Group-I (n = 34) (Isolated NDRD) n (%)	Group-II (n = 11) (NDRD superimposed on underlying DN) n (%)
Acute interstitial nephritis	11 (32.3)	7 (63.6)
Diffuse proliferative glomerulonephritis (post-infectious)	7 (20.5)	-
Membranous nephropathy	4 (11.7)	-
Crescentic glomerulonephritis	4 (11.7)	-
Minimal change disease	2 (5.8)	-
Focal and segmental glomerulosclerosis	2 (5.8)	-
IgA nephropathy	2 (5.8)	-
Amyloidosis	1 (2.9)	-
Lupus nephritis	1 (2.9)	-
Membranoproliferative glomerulonephritis	-	1 (9)
End-stage renal disease	-	3 (27.2)

NDRD: non-diabetic renal disease, DN: diabetic nephropathy

three groups. It was found that patients with isolated DN were younger than patients with NDRD (either isolated or mixed disease). The 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 al also concluded that a shorter duration of diabetes was significantly associated with NDRD.²³ Similar results were reported by Wong, Tone and Huang et al.^{14,28,35} Soni et al from India also reported that a short duration of diabetes was a predictor of NDRD.¹⁶ However, Bertani et al and Mak et al found no significant difference in the duration of diabetes among the different groups.^{24,36} The prevalence of hypertension was similar in all three groups in our study, which is consistent with the findings reported by Soni and Matias et al.^{16,37}

We found that patients with isolated DN as well as those with mixed disease tended to have higher levels of proteinuria compared with the group with isolated NDRD; the difference did not achieve statistical significance. Lin et al also reported lower proteinuria in patients with NDRD thus making it a significant factor indicative of renal biopsy.³² Mak et al found that patients with isolated DN had a higher degree of proteinuria when compared with those with NDRD.²⁴

In this study, the serum creatinine levels were

significantly higher in patients with DN (isolated as well as with superimposed disease) compared with those with NDRD ($P < 0.0001$). Similar results were reported by Matias et al while Soni et al showed that the degree of azotemia was higher in patients having superimposed NDRD.^{16,37} Taft et al reported that in patients with DN, co-existing renal disease was found to be associated with a significantly higher creatinine level, independent of the severity of DN.³⁸ Mak and Lin et al found that patients with both isolated DN and NDRD did not have any difference in serum creatinine levels.^{24,32}

The presence of microscopic hematuria has been suggested by different authors to be one of the atypical features indicating presence of NDRD. Mak and Matias et al found a strong correlation between NDRD and microscopic hematuria.^{24,37} On the contrary, Serra et al reported that DN was most commonly found in diabetic patients manifesting microscopic hematuria.¹⁵ In our study, there was no difference in the prevalence of microscopic hematuria among the three groups. Other authors also found that the frequency of microscopic hematuria was similar in those with DN and NDRD (isolated and superimposed).^{16,32} A Japanese study by Tone showed that microscopic hematuria had lower sensitivity and specificity for the prediction of NDRD compared with the other parameters, suggesting that microscopic

hematuria is not a good predictor of NDRD.²⁸

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 al, who showed that absence of retinopathy was one of the significant factors that predicts NDRD.²³ Tone et al reported that absence of retinopathy showed the highest sensitivity (87%) and specificity (93%) for the prediction of NDRD.²⁸ Similar findings have been reported by others.^{16,26,37} Wong et al showed that absence of retinopathy with hematuria and/or proteinuria ≥ 2 g/day constitutes the most sensitive marker for NDRD and is thus a strong indication for biopsy.¹⁴ However, a few studies have demonstrated lack of correlation between NDRD and presence of retinopathy.^{24,32}

Histologically, NDRD comprised a heterogeneous group in our study. In Group-I patients (isolated NDRD), the most common NDRD was AIN, followed by diffuse proliferative glomerulonephritis, membranous nephropathy and crescentic glomerulonephritis (Table 3). Among Group-II patients also (mixed disorder DN plus NDRD), AIN was the most common lesion. Thus, AIN was the most frequent NDRD seen in 40% of the patients overall (both Group-I and Group-II). In a study from Taiwan, AIN was the most prevalent NDRD (46.5%), followed by membranous nephropathy and IgA nephropathy.³² An Indian study also found AIN to be the most common NDRD, found in 18.1% of the patients with mixed renal disease (NDRD superimposed on DN), while membranous nephropathy (19.2%) was the most frequent diagnosis in patients with isolated NDRD.¹⁶ IgA nephropathy is reported to be the most frequent type of NDRD in the Chinese, Korean and Japanese population with diabetes.^{23,24,28,40} It is important to keep in mind that interstitial inflammatory cell infiltration is often prominent in advanced diabetic glomerulosclerosis. Thus, it is hard to know whether this is secondary to DN or superimposed with AIN, particularly when there is no prominent eosinophil interstitial infiltration. These tubulointerstitial changes in DN are said to be related

to the renal microvascular alterations characteristic of long-term diabetes, and it is now generally held that they are due to chronic ischemia.⁴¹

The pathogenesis of NDRD in patients with diabetes is not well understood. Whether there are common etiologic factors in relation to diabetes or it is merely a coincidence is not clear. Some authors have suggested that the predisposition of DN to superimposed nephritis could be attributed to enhanced exposure of antigenic cellular components, triggering immune responses.⁴⁰ Others, however, found no difference in the prevalence of NDRD between patients with and without diabetes and that the co-existence of a different glomerulonephritis in the diabetic kidney may be merely coincidental.^{11,14,42} The renal outcome in diabetic patients with NDRD varies and depends on the specific type of non-diabetic renal lesion.

We conclude that the prevalence of NDRD, either isolated or superimposed on underlying DN, is high in diabetics with proteinuria. It is recommended that nephrologists maintain a high index of suspicion for performing renal biopsy in diabetic patients. Early diagnosis of NDRD helps in instituting appropriate therapy, which in turn could aid in prolonging renal survival in this patient population.

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