Histopathological evaluation of kidney disease in patients with diabetes mellitus

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Abstract

Introduction: Non-diabetic kidney disease (NDKD), a treatable condition, is common in diabetic patients with atypical clinical presentations. Present study aimed to find out histopathological diagnosis of kidney disease in type 2 Diabetes mellitus (T2DM) with such presentations.

Method: This was a hospital-based cross-sectional study conducted in the Nephrology department, Bir hospital, Nepal from Aug 2019 to January 2021. Total 29 diabetic patients with atypical presentations, the rapid rise of proteinuria alone (n=5), with microscopic hematuria (n=6), with impaired renal function (n=8), and the rapid rise of creatinine with (n=8) or without (n=2) microscopic hematuria were included. The baseline information was recorded and a kidney biopsy was performed.

Result: The mean age of patients was 52.6±10.4 years and 75.9% were male. Diabetic retinopathy (DR) was absent in 82.8% of patients. NDKD was present alone in 20.7% and superimposed on diabetic kidney disease (DKD) in 34.5% with total NDKD in 55.2% and isolated DKD in 44.8% of patients. NDKD were glomerulonephritis(75%) with membranous nephropathy (25%) and IgA nephropathy (25%) patients. The significant difference between NDKD and isolated DKD was only the duration of diabetes < 5 years in 61.5% of isolated DKD and >5 years in 81.2% patients with NDKD (p=0.018). DR was absent in 100% of patients with isolated NDKD, 80% of class III, and 62.5% of class IV DKD.

Conclusion: NDKD is common in T2DM with renal involvement and regardless of retinopathy or duration of diabetes, kidney biopsy should be routinely performed in these patients with atypical clinical presentation.

Keywords: diabetic nephropathy, diabetic retinopathy, hematuria, kidney biopsy, non-diabetic kidney disease, proteinuria
Introduction

Kidney biopsy is not routinely performed in diabetic patients with clinically suspected diabetic kidney disease (DKD) which has an indolent course with gradually and progressively increasing proteinuria and blood pressure and decreasing estimated glomerular filtration rate (eGFR) and is usually associated with diabetic retinopathy. However, histopathological findings in DKD are well documented and classified as class I with mild glomerular basement thickening to class IV with advanced glomerulosclerosis. Kidney biopsies of diabetic patients with atypical clinical presentations (proteinuria without diabetic retinopathy, proteinuria with hematuria, rapid increase of proteinuria, sudden appearance of nephrotic syndrome or nephritic syndrome, and rapid decline of kidney function) had shown the presence of non-diabetic kidney disease (NDKD) alone or superimposed on DKD and isolated DKD. Proteinuric diabetic patients with short duration of diabetes (<5 y), presence of hematuria and absence of diabetic retinopathy (DR) are high likelihood to suffer from NDKD and recommended to undergo kidney biopsy as NDKD might be treatable and curable.

Kidney biopsy of diabetic patients with atypical clinical presentation is a regular practice in our department. However, the biopsy findings in such patients have not been reported yet. So, this prospective study was carried out to evaluate the histopathological diagnosis of kidney disease in such patients.

Method

This was a cross-sectional study carried out in the Department of Nephrology, Bir Hospital from August 2019 to January 2021 after approval from the Institutional Review Board (IRB), National Academy of Medical Sciences (NAMS), Kathmandu, Nepal. All consecutive Type 2 diabetes mellitus (T2DM) patients presenting with an atypical clinical presentation with proteinuria >1 gm/24 h along with either presence of hematuria or absence of retinopathy or rapid increase of proteinuria or rapid increase of creatinine, alone or in combination during the study period were included. Patients with urinary tract infection, single kidney, and chronic kidney disease (CKD) stage 5 were excluded. Patients were explained about the possibility of NDKD and the need for kidney biopsy, the procedure detail and its complications like pain and hematuria, and its management immediately as per departmental protocol, and written informed consent was taken.

The baseline information like age, gender, duration of diabetes, duration of hypertension, presence or absence of diabetic retinopathy, urinary albumin and red blood cells/HPF, fasting and 2 h postprandial blood sugar, glycated hemoglobin, urea, creatinine, 24-h urinary protein, kidney size and echotexture in ultrasound abdomen and blood pressure were recorded.

Patients presenting with acute kidney injury (AKI) and acute nephritic presentation (proteinuria, hematuria, rising creatinine with decreased urine output, and swollen body) were admitted immediately and managed, whereas other patients were admitted on an elective basis. Patients without a history of treatment for DR were sent to an ophthalmologist for retina check-ups and the reports were recorded. All patients were advised for serology (HBsAg, HIV, Anti HCV) and bleeding profile as a prerequisite for kidney biopsy. Other serological tests like Antinuclear antibody (ANA), anti-double-stranded DNA (anti-Ds DNA), Complement 3 and Complement 4, anti-neutrophil cytoplasmic antibodies were sent only in patients with clinical indication. The estimated glomerular filtration rate (eGFR) was calculated by using abbreviated MDRD (modification of diet in renal disease) equation $186 \times (\text{creatinine}/88.4) - 1.154 \times (\text{age}) - 0.203 \times (0.742 \text{ if female}) \times (1.210 \text{ if black})$. A kidney biopsy was performed after admission as a bedside procedure with ultrasound-guided technique. Patients were kept in a prone position lying with their
abdomen on a firm pillow below the umbilicus to straighten the lumbar spine & to splint the kidneys. Ultrasound with a 3.5 MHz transducer was used to localize the surface marking of the lower pole of the left kidney. The distance to the biopsy point from the skin surface was assessed and the surface was marked at the expected needle entry point. The biopsy was performed by continuous (real-time) ultrasonic guidance with an automated biopsy needle (Bard with Gauge size of 18G and needle length of 16cm). Three pieces of kidney tissues were obtained in different containers for light microscopic, immunofluorescence, and electron microscopic examination. After the biopsy, all patients were kept on bed rest for 12-h and monitored regularly for complications, and managed as per hospital protocol. Patients were discharged the next day and followed up with histopathological reports and the diagnosis was recorded as NDKD with specific diagnosis and DKD with histopathological class according to Renal Pathology Society Classification as follows.2

Class I: Isolated glomerular basement membrane thickening. Basement membranes are greater than 430 nm in males older than age 9 and 395 nm in females. There is no evidence of mesangial expansion, increased mesangial matrix, or global glomerulosclerosis involving >50 percent of glomeruli.

Class II: Mild (class IIa) or severe (class IIb) mesangial expansion. A lesion is considered severe if areas of expansion larger than the mean area of a capillary lumen are present in >25 percent of the total mesangium.

Class III: At least one Kimmelstiel-Wilson lesion (nodular intercapillary glomerulosclerosis) is observed on biopsy and there is <50 percent global glomerulosclerosis.

Class IV: Advanced diabetic sclerosis. There is >50 percent global glomerulosclerosis that attributable to diabetic nephropathy.

All patients were treated and followed up regularly according to diagnosis and clinical presentation.

Result

Total twenty-nine T2DM patients with atypical clinical presentation alone or in combination had undergone kidney biopsy during this study period. None of the patients were biopsied for unexplained CKD or AKI presenting without proteinuria.

Proteinuria was non nephrotic (<3.5 gm/24 h) in 7(24.1%) and nephrotic (>3.5 gm/24 h) in 22(75.9%) patients. Diabetic retinopathy was absent in 24(82.8%) and microscopic hematuria was present in 14(48.3%) patients. Other atypical clinical presentations were the rapid rise of proteinuria alone 5(17.2%) with microscopic hematuria 6(27.6%), and the rapid rise of creatinine with 8(27.6%) and without 2(6.9%) microscopic hematuria (Table 1). A history of hypertension was present in 26(89.7%) and 12(14.4%) patients had high blood pressure at presentation.

The mean age (y) of patients were 52.6±10.4 (range 33-72) with 22(75.9%) male and median (range) duration of diabetes, hypertension, serum creatinine, eGFR and urine total protein (UTP) were 7(range 1-25) y, 1.5(range 0-25) y, 2.0(range 0.9-8.6) mg/dl, 30.3(range 6.7 - 91.5) ml/min/1.73m² and 5.6(range 1.1-16.4) gm/24 h respectively.

Kidney biopsy had shown NDKD in 16 (55.2%) and isolated DKD in 13(44.8%) patients. The NDKD were glomerulonephritis 12(75%) and hypertensive kidney disease 4(25%). The commonest glomerulonephrites were membranous nephropathy 4(25%) and IgA nephropathy 4(25%) as shown in Table 2. Isolated NDKD was present in 6(20.7%), superimposed on DKD in 10(34.5%) patients with total DKD in 23(79.3%) patients. The histopathological class of DKD was class Ila in 3(13%), IIb in 2(8.7%) and pathognomonic lesion of DKD (Kimmelstiel-Wilson nodule) was present in 18(78.3%) patients with 10(43.5%) belonged to class III and 8(34.8%) belonged to class IV, Figure 1.

Baseline clinical and laboratory parameters between patients with NDKD and isolated DKD
had shown no significant difference except the duration of diabetes which was <5 y in 8(61.5%) of isolated DKD and ≥ 5 y in 13(81.2%) patients with NDKD (p=0.018) as shown in Table 3. On further analysis, 4(66.7%) patients with isolated NDKD had a duration of diabetes 5 - 10 y. Among patients with DKD, the duration of diabetes was <5 y in 1(20%) of class II, 5(50%) of class III, and 3(37.5%) patients with class IV with no significant (p=0.750) difference between the classes.

Microscopic hematuria was present in 4(30.8%) patients with isolated DKD and two of them also had a rapid rise of creatinine. Diabetic retinopathy was absent in 100% of patients with isolated NDKD, DKD class Ila and Ilib, 80% of class III, and 62.5% of class IV. Analysis of the pattern of disease according to atypical presentation had shown the presence of both NDKD and DKD in patients with all presentations. The clinical presentations were the rapid rise of proteinuria with renal impairment in 6(46.2%) patients with isolated DKD and the rapid rise of creatinine with microscopic hematuria in 6(50%) patients with glomerulonephritis.

**Table 1. Indication of kidney biopsy in type 2 diabetic patients with atypical presentation (N=29)**

| Atypical clinical presentation | Diabetic retinopathy | Total |
|-------------------------------|----------------------|-------|
|                               | Absent | Present |       |
| The rapid rise of proteinuria |         |         |       |
| Alone                         | 4      | 1       | 5     |
| With microscopic hematuria    | 5      | 1       | 6     |
| With impaired renal function  | 5      | 3       | 8     |
| The rapid rise of creatinine  |         |         |       |
| With microscopic hematuria    | 8      | 0       | 8     |
| Without microscopic hematuria | 2      | 0       | 2     |
| Total                         | 24     | 5       | 29    |

**Table 2. Histopathological diagnosis of non-diabetic kidney disease (N=16)**

| Histopathological diagnosis | Isolated | On DKD | Total |
|----------------------------|----------|--------|-------|
| Glomerulonephritis (GN) (n=12) |          |        |       |
| Membranous GN               | 2        | 2      | 4 (13.8%) |
| IgA nephropathy              | 1        | 3      | 4 (13.8%) |
| PIGN                        | 0        | 2      | 2 (6.9%)  |
| FSGS                        | 1        | 0      | 1 (3.45%) |
| Cryoglobulinemia            | 1        | 0      | 1 (3.45%) |
| Hypertensive Kidney Disease | 1        | 3      | 4 (13.8%) |
| Total NDKD                  | 6 (20.7%)| 10 (34.5%) | 16 (55.2%) |

PIGN –Postinfectious GN, FSGS – Focal segmental glomerulosclerosis

**Figure 1. Histopathological class of isolated DKD (N=13) and NDKD on DKD (N=10)**
Juju Raj Shrestha: Kidney biopsy findings in diabetes

Table 3. Comparison of baseline clinical and laboratory parameters between patients with NDKD and DKD

| Parameter                  | NDKD (n=16) | DKD (n=13) | p value |
|----------------------------|-------------|------------|---------|
| Age (y)*                   | 54.2±12.8   | 51.3±8.0   | 0.49    |
| Male gender n(%)           | 9 (69.2%)   | 13 (81.3%) | 0.37    |
| SBP (mm Hg)*               | 133.1±20.2  | 128.8±15.4 | 0.52    |
| DBP (mm Hg)*               | 81.5±8.0    | 77.50±10.0 | 0.24    |
| FBS (mg/dl)*               | 126.4±33.1  | 127.8±20.0 | 0.89    |
| PPBS (mg/dl)*              | 188.5±27.4  | 191.3±34.9 | 0.81    |
| Serum creatinine (mg/dl)†  | 1.8 (0.9-6.3)| 2.4(0.9-8.6)| 0.26    |
| eGFR (ml/min/1.73m²)†      | 42.4 (10.5-91.5)| 29.1 (6.7-88.2)| 0.26    |
| UTP (gm/24 h)†             | 4.64 (1.2 -16.4)| 5.83(1.1-16.0)| 0.20    |
| Duration of diabetes (y)†  | 7.5 (1-20)  | 4.0 (3-25) | 0.60    |
| Duration of hypertension (y)†| 3.0 (0-20)  | 1 (0-25)   | 0.58    |
| Duration of diabetes <5 y  | 3 (18.8%)   | 8 (61.5%)  | 0.018   |
| ≥5 y                       | 13 (81.2%)  | 5 (38.5%)  |         |
| Diabetic retinopathy n(%)  | 2 (12.5%)   | 3 (23.1%)  | 0.63    |
| Present                    | 14 (87.5%)  | 10 (76.9%) |         |
| Absent                     | 10 (62.5%)  | 4 (30.8%)  | 0.13    |

*Mean±SD  *Median (Range); SBP: systolic blood pressure; DBP: diastolic blood pressure; FBS: fasting blood sugar; PPBS: 2h postprandial blood sugar; eGFR: estimated glomerular filtration rate; UTP: urine total protein

Discussion

Diabetic kidney disease is one of the commonest complications of diabetes and one of the important causes of CKD.8 However, patients with diabetes may have NDKD in isolation or combination with DKD.9 We conducted a cross-sectional study among 29 diabetic patients with atypical clinical presentations and performed a kidney biopsy to find out the histopathological diagnosis.

Proteinuria was present in all patients and the indications of kidney biopsy were the rapid rise of proteinuria in 65.5% and a rapid rise in serum creatinine in the remaining. This was not similar to the study reported by Soni, et al.10 who reported the common indications for kidney biopsy in diabetics were nephrotic syndrome in 34.4%, AKI in 30.6%, and rapidly progressive renal failure in 15% of patients.

In our study, 55.2% of the study population had NDKD, of which 20.7% had isolated NDKD and 34.5% had NDKD superimposed on DKD and 44.8% had isolated DKD. Glomerulonephritis was present in 75% and hypertensive nephrosclerosis in 25% of patients with NDKD. Membranous nephropathy (MN) and IgA nephropathy were the commonest glomerular disease followed by PIGN, focal segmental glomerulosclerosis (FSGS), and cryoglobulinemia in our patients. A retrospective study in Kuwait in diabetic patients showed 54.8% had isolated DKD whereas 45.2% patients had NDKD superimposed on DKD and no patient had isolated NDKD.5 Similarly, a Turkish study reviewed 48 kidney biopsies from patients with T2DM and found NDKD in 58.3% (NDKD alone in 50% and superimposed on DKD in 8.3%). The most common diagnosis was MN, tubulointerstitial nephropathy, IgA nephropathy, and FSGS.11 There are wide geographical and population-wide variations in the occurrence of DKD, NDKD, or NDKD plus DKD. An Indian study12 reported the prevalence of NDKD in North India to be 12.3%, while John, et al.13 reported a higher prevalence of NDKD (81.2%) in South India with proliferative glomerulonephritis in 46% of patients with NDKD. However, studies from the USA had revealed FSGS as the commonest GN affecting 18.8% to 22% of patients with NDKD.14,15 Furthermore, patients with NDKD had slower progression to end-stage renal disease compared with patients who had DKD alone, probably due to disease-specific therapies aimed at their primary etiologies.11
Among our patients with DKD, the histopathological lesion was class III in 43.5% and class IV in 34.8% which was similar to the study reported by Zajjari, et al.\textsuperscript{16} showing class III in 42.3% and class IV in 34.6% and they had suggested that the higher histological classes are associated with lower eGFR and more likely to be associated with DR and nephrotic proteinuria. However, the association and chronology of appearance of DKD and retinopathy in T2DM are not well defined,\textsuperscript{17} but a probable role for DR in predicting DKD has been postulated,\textsuperscript{18} and absence of DR is considered an indication of kidney biopsy in diabetic patients with albuminuria.\textsuperscript{1} The major reason put forward for the coexistence of DR and DKD is dilation in retinal vessels and DR reflective of cumulative microvascular damage which can eventually result in DKD. These microvascular damages could result from different mechanisms including inflammation and oxidative stress. Inflammation that is associated with wider retinal venular caliber,\textsuperscript{19} also contributes to the development and progression of DKD, through the increased expression of inflammatory-associated mediators.\textsuperscript{20} Another mechanism enmeshes advanced glycation end products (AGEs) that are synthesized during high oxidative stress or hyperglycemia. AGEs can lead to cellular hypertrophy and apoptosis in the kidney,\textsuperscript{21} and calcification and apoptosis in the eye.\textsuperscript{22} High serum AGE levels, as found in patients with CKD, have been shown to trigger retinopathy to a comparable extent as that seen in people with diabetes.\textsuperscript{23} The vascular damages occurring in the eyes could therefore reflect at early stages vascular damages in the kidney. Hsieh, et al.\textsuperscript{6} reported that patients with isolated DKD had a significantly higher prevalence of retinopathy compared to patients with NDKD±DKD (83.3% vs 30%, p<0.001). In the present study, DR was absent in 82.8% of patients. Comparison of prevalence of DR between patients with NDKD±DKD and isolated DKD showed its presence in 12.5% of former and 23.1% of latter with no significant difference. Moreover, DR was absent in 80% of class III and 62.5% of class IV DKD implying that retinopathy was not a good predictor of DKD even in advanced kidney involvement in our diabetic population.

The patients with DKD and NDKD had no significant difference in age, BP, eGFR, proteinuria or duration of diabetes, or presence of retinopathy. However, when the study population was grouped into diabetes with a duration of 5 y or more, there was a significantly higher number of DKD in those who had diabetes for <5 y and higher NDKD in those who had diabetes for ≥5 y, (p=0.018). The natural history of DKD in Type 1 Diabetes has shown slow progression with the appearance of dipstick positive proteinuria after 10 – 15 y of onset of diabetes. It is postulated to follow the same course in T2DM also. However, as T2DM might remain asymptomatic for many years, they might have proteinuria and DKD on kidney biopsy even before a diagnosis of diabetes.\textsuperscript{24} In a study to describe a stepwise approach for the timing of kidney biopsy in T2DM had concluded that patients with proliferative DR were more likely to have DKD and kidney biopsy could be avoided, patients without DR and short duration diabetes (<5 y) were highly likely to would to have NDKD and kidney biopsy have to be performed and patients without DR and duration of diabetes (≥5 y) were likely to have NDKD and kidney biopsy might be considered.\textsuperscript{6} In our study, all patients had overt proteinuria of >1 gm/24 h and DR was absent in 24(82.6%) with significantly higher DKD in patients of a short duration of DM (<5 y) contradict the previous findings of a significant short duration of diabetes in patients with NDKD than DKD\textsuperscript{3,6,25} and it could be due to late diagnosis of diabetes in our patients. Moreover, the glomerular changes in DKD progress with the duration of diabetes and often correlate with clinical presentation\textsuperscript{26,27} An autopsy study has shown the presence of histological proven DKD in patients without proteinuria and renal impairment suggesting the possibility of DKD even before clinical findings and there was a significantly higher duration of diabetes with advancing DKD class. However, the short duration of diabetes (<5 y) in 20% patients with class II, 50% patients with class III, and 37.5% with Class IV DKD with no significant difference
of duration of diabetes between the DKD classes suggests the possibility of initiation of histological changes long before the diagnosis of diabetes in our population.

Evaluation of histopathological diagnosis according to clinical presentations had shown an association of DKD with the presence of DR and severe proteinuria. Absence of DR plus nephritic or nephrotic presentation had 90% and unexplained renal failure had a 69% positive predictive value for NDKD. In our study, we found glomerulonephritis as the commonest NDKD in patients presenting with a rapid rise in creatinine with microscopic hematuria and isolated DKD in patients with a rapid rise in proteinuria with renal impairment irrespective of the status of DR.

Conclusion

The present study has shown glomerulonephritis as the commonest NDKD in type 2 DM with atypical clinical presentation and advanced DKD (Class III & IV) is present even in absence of diabetic retinopathy and short duration of diabetes.

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Conflict of Interest

None

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None

Author Contribution

Concept, design, planning: AB; Literature review: JRS; Data collection: JRS; Data analysis: RH; Draft manuscript: JRS; Revision of draft: KD; Final manuscript: JRS, RH; Accountability of the work: JRS.

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