Original Article

Renal Histology in Diabetic Patients

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Abstract

Background: The diagnosis of diabetic nephropathy is based on the course of clinical manifestations and renal biopsy. Renal biopsy is usually performed in patients with atypical presentations.

Objectives: This study was performed to analyze various renal histopathological lesions in diabetic patients and to establish a clinicopathological correlation.

Materials and Methods: In this retrospective study, the authors analyzed renal histology of 40 patients with type 2 diabetes mellitus who presented with atypical features of diabetic renal involvement and underwent renal biopsy at the Military Hospital Mohammed V, Rabat, Morocco, between January 2008 and December 2016.

Results: About 60% of the patients had isolated diabetic nephropathy, 35% had isolated nondiabetic renal diseases and 5% had both. Patients with nondiabetic renal diseases had significantly higher hematuria ($P = 0.02$), shorter duration of diabetes ($P = 0.009$), higher mean estimated glomerular filtration rate ($P = 0.04$) and lower prevalence of diabetic retinopathy ($P < 0.001$). The most common histological lesion in patients with nondiabetic renal diseases was IgA nephropathy (25%). In patients with diabetic nephropathy, the most common histological class was Class III (42.3%). Furthermore, higher histological classes were associated with lower estimated glomerular filtration rate ($P < 0.001$) as well as higher prevalence of diabetic retinopathy ($P = 0.009$) and nephrotic proteinuria ($P = 0.04$).

Conclusions: This study found that in Rabat, Morocco, the most common histopathological lesion in patients with diabetes was diabetic nephropathy. Hematuria, shorter duration of diabetes, higher mean estimated glomerular filtration rate and lower prevalence of diabetic retinopathy were reported among those with nondiabetic renal diseases. These findings are in accord with that of studies from other countries. However, large sample size and long-term follow-up clinical studies are needed to demonstrate the renal pathological implications and renal outcomes in type 2 diabetes mellitus patients with renal involvement.

Keywords: Diabetic nephropathy, Morocco, nondiabetic renal disease, pathological classification, renal biopsy, type 2 diabetes

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INTRODUCTION

The prevalence of diabetes in the adult general population of Morocco has been found to vary from 6.6% to about 17%, suggesting that diabetes mellitus (DM) is a major public health problem.[1,2] Diabetic nephropathy (DN) is the most common cause of end-stage renal disease worldwide.[3] Epidemiologic studies have shown that DN is strongly clustered in families and that race has a major effect on DN susceptibility and rate of progression, firmly establishing the importance of genetic risk factors in the

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development of DN.[4] According to Bos and Agyemang,[5] in Egypt, the prevalence of nephropathy in diabetic patients ranged from 6.7% in outpatient clinics to 46.3% in inpatients. However, in the EpiDiaM cohort study that included 1196 diabetic patients from outpatient clinics in Morocco, the prevalence of nephropathy was found to be low (4.8%).[6]

The treatment and prognosis of DN and nondiabetic renal disease (NDRD) are different, and renal biopsy is necessary to differentiate the two. However, renal biopsy is generally not carried out as a routine diagnostic test in a typical clinical DN presentation. Nonetheless, the histological lesions of DN have a characteristic pattern that can be identified by light microscopy (LM) and electron microscopy (EM). Apart from changes in the glomeruli, abnormalities are found in the tubulointerstitial and vascular compartments.

Pathological classifications exist for several renal diseases, but a uniform classification for DN was lacking until, in 2010, Tervaert *et al*.[7] presented a pathological classification of DN. However, to date, limited studies have analyzed the relationship between histological and clinical findings according to this classification system. Therefore, the aim of this study was to evaluate various renal histopathological lesions in diabetic patients and to establish a clinicopathological correlation.

MATERIALS AND METHODS

This retrospective study included all type 2 DM patients, diagnosed using the American Diabetes Association criteria,[8] who presented with atypical features of diabetic renal involvement and underwent renal biopsy between January 2008 and December 2016 at the Military Hospital Mohammed V, Rabat, Morocco.

Atypical features of renal involvement include the sudden onset of massive proteinuria; active urine sediment, proteinuria in the absence of retinopathy or in diabetes of short duration and rapidly deteriorating renal function. All biopsies were performed by nephrologists under ultrasonographic guidance using a 16-G renal biopsy needle. Two cores of renal tissue were obtained: one was sent for LM and the other for immunofluorescence studies. EM was not performed because of its nonavailability. The LM sections were stained using hematoxylin and eosin, periodic acid–Schiff, Masson's trichrome and Jones silver stains. The immunofluorescence sections were stained using anti-human IgA, IgM, IgG, C3, C1q, fibrinogen and kappa- and lambda light chains.

The authors examined these stains, and based on the histology findings, three groups were defined: Group A, isolated DN; Group B, isolated NDRD; and Group C, NDRD superimposed on underlying DN. The glomerular lesions were classified according to the classification of DN proposed by Tervaert *et al*.[7] Tubulointerstitial and vascular scores were also graded. Two pathologists reviewed the slides with total concordance among the different classes. The glomerular classification of DN were as follows: Class I, isolated the thickening of the glomerular basement membrane; Class IIA, mild mesangial expansion; Class IIB, severe mesangial expansion; Class III, Kimmelstiel–Wilson nodular lesion; and Class IV, advanced glomerulosclerosis.

A fundus examination was also performed in all patients by an ophthalmologist for diagnosing diabetic retinopathy (DR). In addition to the slides, the authors analyzed the following clinical and laboratory parameters: age, gender, duration of diabetes, presence or absence of hypertension, presence or absence of hematuria, retinal finding on fundus examination, estimated glomerular filtration rate (eGFR), urine examination, 24-h urine protein estimation and glycated hemoglobin.

In this study, none of the patients received treatments such as steroids or immunosuppression that could have altered the presentation (i.e., quantity of proteinuria and eGFR). However, all patients with high blood pressure were treated with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers.

Statistical analysis was performed using SPSS 19 (IBM Corp., Armonk, NY, USA). Numerical data were expressed as mean ± standard deviation and categorical data in percentage and numerical values. Differences between groups were assessed using the univariate Chi-square test for categorical variables, and means were compared using ANOVA tests. $P < 0.05$ was considered to be statistically significant.

Ethical approval for this study (MMTH/IEC30/07-2018-16) was provided by the Institutional Ethical Committee of Mohammed V Military Teaching Hospital, Rabat, Morocco, on July 16, 2018. This study was carried out in accordance with the Declaration of Helsinki, 2013.

RESULTS

In this study, 40 type 2 DM patients presented with atypical features of diabetic renal involvement and underwent renal biopsy. Of these, 30 (75%) patients were male, and the mean age was 57.5 ± 7.28 years (range 45–79 years).

Further, 24 (60%) patients were found to have isolated DN (Group A) and 16 (40%) had NDRD either alone or superimposed on DN (Groups B and C) [Table 1]. Hypertension was noted in 26 (65%) patients. The mean duration of diabetes was 8.8 ± 7.42 years; the mean 24-h urine protein was 5.08 ± 2.83 g/day and eGFR was 35.88 ± 26.05 ml/min/1.73 m^2.

The duration of DM was significantly shorter in Group B than in Group A (P = 0.009), and eGFR was also significantly higher in Group B than in Group A (P = 0.04). Further, DR was significantly higher in Group A than in Group B ($P \leq 0.001$) and hematuria was significantly higher in Group B than in Group A (P = 0.02). However, there was no difference between the three groups with respect to mean age, percentage of males, dyslipidemia, hypertension and treatment with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers [Table 2].

The histological lesions observed in Groups B and C are summarized in Table 3. The most common histological lesion was IgA nephropathy (four cases) followed by membranous nephropathy (three cases). Of the four IgA nephropathy cases, three were associated with simultaneous systemic symptoms (purpuric skin rash and arthritis) of Henoch–Schönlein purpura (HSP).

In DN patients (Groups A and C), the most common histological class was Class III (11 cases; 42.3%) followed by Class IV (9 cases; 34.6%), Class IIA (4 cases; 15.3%) and Class IIB (2 cases; 7.6%). The clinical and laboratory parameter comparison between these classes is presented in Table 4. Higher histological classes were significantly associated with lower eGFR ($P \leq 0.001$) as well as higher prevalence of DR (P = 0.009) and nephrotic proteinuria (P = 0.04). No statistically significant association was found for the other analyzed factors.

Tubulointerstitial and vascular scores of these groups were also compared [Table 5] and it was found that the interstitial fibrosis and tubular atrophy (IFTA), interstitial inflammation and arteriosclerosis scores in Class IV patients were greater than those of other groups.

Table 1: Demographic data

Variables	Group A (n = 24)	Group B (n = 14)	Group C (n = 2)	P
Age (years ± SD)	57.16 ± 7.87	57.35 ± 6.66	62.5 ± 3.5	0.61
Male, n (%)	19 (79.16)	10 (71.4)	1 (50)	0.61

Group A – Patients with isolated diabetic nephropathy; Group B –Patients with isolated nondiabetic renal diseases; Group C – Nondiabetic renal disease superimposed on underlying diabetic nephropathy; SD – Standard deviation

DISCUSSION

In patients with DM, treatment options and prognosis differ between those with DN and NDRD. Therefore, renal biopsy should be carried in atypical renal presentations such absence of DR; low or rapidly decreasing eGFR; rapidly increasing proteinuria or nephrotic syndrome; presence of active urinary sediment; or signs or symptoms of other systemic disease.[9,10] Although Tervaert *et al*.[7] presented a pathological classification of DN, few studies have established a correlation between histological and clinical findings according to this classification system. Using this classification, the current study found that 60% of type 2 diabetic patients with atypical features of diabetic renal involvement had isolated DN (Group A).

NDRD was reported in 40% of renal biopsies from type 2 diabetic patients. This is in accordance with the findings of the previous studies, where the prevalence of NDRD was found to range from 45% to 57%.[10-15] In contrast, a meta-analysis revealed that NDRD was reported in 22% of European and 26.7% of Asian patients with type 2 DM. Thus, even after adjusting for differences in methodology among the studies, NDRD was found to affect a significant percentage of patients with type 2 DM.[16] The variation in NDRD prevalence across studies could be due to selection bias in indications for biopsy and differences in population studied. Nonetheless, the findings of these studies and that of the current study collectively suggest

Table 2: Comparison of various parameters between different types of nephropathies

Parameters	Group A (n = 24)	Group B (n = 14)	Group C (n = 2)	P
Diabetes duration (years ± SD)	11.62 ± 8.18	4.42 ± 3.15	5.50 ± 0.70	0.009
Diabetic retinopathy, n (%)	18 (75)	2 (14.2)	0	0.001
Proteinuria (g/day ± SD)	4.88 ± 2.62	5.65 ± 3.33	3.50 ± 0.70	0.53
Hematuria, n (%)	10 (41.66)	12 (85.71)	1 (50)	0.02
Hypertension, n (%)	18 (75)	7 (50)	1 (50)	0.26
Dyslipidemia, n (%)	15 (62.5)	9 (64.28)	0	0.20
eGFR (±SD) (ml/min/1.73 m^2)	28.38 ± 18.6	49.85 ± 32.84	28 ± 16.97	0.04
Mean HbA1c (percentage ± SD)	7.79 ± 1.98	7.97 ± 1.32	7 ± 0	0.76

Group A – Patients with isolated diabetic nephropathy; Group B – Patients with isolated nondiabetic renal diseases; Group C – Patients with nondiabetic renal disease superimposed on underlying diabetic nephropathy; SD – Standard deviation; eGFR – Estimated glomerular filtration rate; HbA1c – Glycated hemoglobin

that NDRD frequently occurs in type 2 DM patients with renal involvement.

In this study, the most common histological lesion was IgA nephropathy (25.1%) followed by membranous nephropathy (18.8%); these findings are comparable with that reported by Zhou *et al*.[17] HSP infrequently occurs in adults; however, special attention should be given to HSP in cases with renal involvement because it can worsen the prognosis. In this study, three cases of HSP were reported; to best of the authors' knowledge, only few cases of HSP associated with diabetes have previously been reported in the literature.[18-20]

The results of the current study showed that the duration of diabetes was significantly lower in the isolated NDRD group, indicating that patients with shorter duration of diabetes are at a higher risk for NDRD. Similar results were also reported in other studies.[21-25] In contrast, Mak *et al*.[9] and Bertani *et al*.[26] did not find difference in the duration of diabetes between DN and NDRD groups.

This study found hematuria to be more commonly observed among type 2 DM patients with NDRD than those with DN. Similarly, a strong correlation between NDRD and microscopic hematuria has been reported in various studies.[17] In the current study, the frequency of hypertension was comparable between all groups, a finding similar to that reported by Soni *et al*.[27] In contrast, Zhou *et al*.[17] reported that the mean systolic blood pressure was higher in type 2 DM patients with DN than those with NDRD.

In type 2 DM, the prevalence of DR varies from 40% to 75%.[10] DR is more frequently seen in patients with DN and its absence is an important predictor of NDRD;[22,27] similarly, DR was absent in 87.5% of patients with NDRD in the current study. According to Wong *et al*.,[28] the absence of DR along with hematuria and/or proteinuria ≥2 g/day constitute the strongest indication of NDRD. Thus, these indicators collectively are more sensitive predictors of NDRD than any one of them alone.

In our study, eGFR was significantly higher in patients with NDRD than in patients with DN. Similar results were reported by Matias *et al*.[29] and Yaqub *et al*.[30] However, Soni *et al*.[27] showed that the degree of azotemia was higher in patients with NDRD superimposed on DN than in either of the isolated groups (i.e., Groups A and B). This discrepancy in eGFR may be explained by the low frequency of mixed lesions ($n = 2$; 5%) in the current study. Therefore, the current study data may not be sufficiently

Table 3: Histological diagnosis in patients with nondiabetic renal diseases

Histology	Group B ($n = 14$), n (%)	Group C ($n = 2$), n (%)
Henoch-Schönlein purpura	2 (12.5)	1 (6.3)
Membranous nephropathy	3 (18.8)	-
Myeloma cast nephropathy	1 (6.3)	1 (6.3)
Postinfectious glomerulonephritis	2 (12.5)	0
Lupus nephritis	2 (12.5)	0
Amyloidosis AA	1 (6.3)	0
IgA nephropathy	1 (6.3)	0
Minimal change disease	1 (6.3)	0
Focal segmental glomerulosclerosis	1 (6.3)	0

Group B – Patients with isolated nondiabetic renal diseases; Group C – Patients with nondiabetic renal disease superimposed on underlying diabetic nephropathy

Table 4: Clinical and biochemical parameters across different classes of diabetic nephropathy

Parameter	Class IIA ($n = 4$)	Class IIB ($n = 2$)	Class III ($n = 11$)	Class IV ($n = 9$)	*P*
Mean age of patients (years ± SD)	57 ± 6.68	58.5 ± 3.53	56.45 ± 6.72	59 ± 10.34	0.91
Mean duration of diabetes (years ± SD)	4.75 ± 1.25	3.5 ± 2.12	11.9 ± 4.63	14.77 ± 11.07	0.08
Hypertension, *n* (%)	2 (50)	1 (50)	8 (72.72)	8 (88.88)	0.42
Hematuria, *n* (%)	1 (25)	1 (50)	6 (54.54)	3 (33.33)	0.68
Nephrotic syndrome, *n* (%)	1 (25)	2 (100)	10 (90.90)	7 (77.77)	0.04
Mean proteinuria levels (g/day ± SD)	2.75 ± 0.95	4.50 ± 2.12	4.68 ± 1.61	5.86 ± 3.57	0.24
Mean eGFR (ml/min/1.73 m^2 ± SD)	35 ± 12.93	55.55 ± 7.77	35.63 ± 15.22	10.46 ± 5.60	<0.001
Mean HbA1c (percentage ± SD)	7.25 ± 0.50	6.50 ± 0.70	8.23 ± 2.67	7.60 ± 1.23	0.62
Diabetic retinopathy, *n* (%)	0	2 (100)	8 (72.72)	8 (88.88)	0.009

SD – Standard deviation; eGFR – Estimated glomerular filtration rate; HbA1c – Glycated hemoglobin

Table 5: Pathological details across different classes of diabetic nephropathy

Parameter	Class IIA ($n = 4$)	Class IIB ($n = 2$)	Class III ($n = 11$)	Class IV ($n = 9$)	*P*
Mean number of glomeruli ± SD	10 ± 0	12 ± 0	18.90 ± 14.45	15.66 ± 3.77	0.45
Percentage of glomerulosclerosis ± SD	20 ± 8.16	15 ± 7.07	34.72 ± 15.45	48.88 ± 20.88	0.01
Mean IFTA score ± SD	0.75 ± 0.5	1 ± 0	1.63 ± 0.67	2.55 ± 0.52	<0.001
Mean ITA score ± SD	0	0	0.54 ± 0.52	1 ± 0	<0.001
Mean arteriolar hyalinosis score ± SD	0.75 ± 0.5	0.5 ± 0.7	0.72 ± 0.64	0.88 ± 0.6	0.85
Mean arteriosclerosis score ± SD	0.5 ± 0.57	0	1 ± 0.44	1.44 ± 0.52	0.002

IFTA – Interstitial fibrosis and tubular atrophy; ITA – Interstitial inflammation; SD – Standard deviation

accurate for analyzing the clinical features and renal outcomes of Group C patients.

Renal biopsy determines the extent of damage in DN, and it is useful in detecting renal diseases other than those caused by diabetes.[31] The current study correlated the histological features in DN with the clinical and laboratory parameters in accordance with the classification by Tervaert *et al*.[7] In the literature, only few studies have classified DN according to this classification. To the best of the authors' knowledge, the current study is the first study from Morocco to classify cases of DN based on this classification. Afroz *et al*.[32] found that in diabetic patients from a tertiary referral hospital in India, Class III glomerular lesions were most common, accounting for 50% of all lesions. Similarly, the current study also found Class III glomerular lesions to be the most common, constituting about 42% of all lesions.

The mean duration of DM in Classes IIA, IIB, III and IV was 4.75 ± 1.25, 3.5 ± 2.12, 11.9 ± 4.63 and 14.77 ± 11.07 years, respectively. There was no significant correlation between the duration of diabetes and class of DN ($P = 0.08$). These findings are in contrast with that of Schwartz *et al*.[33] who found a statistically significant difference in the duration of diabetes between patients with Kimmelstiel–Wilson (Class III) and mesangial (Class IIB) lesions.

In this study, of the 18 patients with DR and DN, 16 (88.8%) patients belonged to Classes III and IV and 2 to Class IIB. Therefore, the presence of DR is correlated with higher classes of DN ($P = 0.009$). These findings are similar to that of Harada *et al*.,[15] who found that the more severe renal lesions (Class III and IV) are observed in patients with both DR and DN than in patients without DR. In the current study, higher classes of DN were found to be associated with nephrotic proteinuria ($P = 0.04$). Similar observations were noted in the study by Mise *et al*.,[34] where the severity of proteinuria was correlated with the index of structural lesions.

The current study found that lower eGFR was associated with higher DN classes ($P < 0.001$). This finding is in agreement with that of Schwartz *et al*.,[33] who found that creatinine clearance was significantly lower in patients with nodular sclerosis lesions than in patients with mesangial lesions. Mise *et al*.[34] analyzed the renal biopsy of 205 patients with type 2 diabetes and found that in the higher glomerular classes, tubulointerstitial and vascular lesions was associated with renal endpoint. Therefore, the pathological classification of DN is important for predicting the renal prognosis.[34] In the current study, the most common histological class was Class III ($n = 11$ cases) followed by Class IV ($n = 9$ cases). Further, a high score of IFTA, interstitial inflammation and arteriosclerosis was observed in higher classes. Therefore, the results of this study suggest a poor renal prognosis in patients with DN.

This study had several limitations. First, it had a relatively small sample size. Second, this was a retrospective cohort study and indications for renal biopsy were not standardized. Finally, EM was not performed due to its nonavailability. Therefore, additional prospective regional studies are needed for further defining the prevalence of NDRD and clarifying the factors of renal prognosis.

CONCLUSIONS

In this study, the most common histopathological lesion in patients with type 2 DM and renal dysfunction was DN. Further, Class III glomerular lesions were most common. Higher histological classes were associated with lower eGFR and more likely to be associated with retinopathy and nephrotic proteinuria. The most common histological lesion in NDRD patients was IgA nephropathy. This study also found that shorter duration of diabetes, hematuria, absence of retinopathy and higher eGFR can predict NDRD. Large sample size and long follow-up clinical studies are needed to demonstrate the renal pathological implications and outcomes in type 2 DM patients with renal involvement.

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Conflicts of interest
There are no conflicts of interest.

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