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Jacobs Journal of Nephrology and Urology

Original Article

Histopathological Findings of Patients with Type 2 Diabetes Undergoing Kidney Biopsy: Diabetic Nephropathy versus Non-Diabetic Kidney Disease

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Received Date: 02-28-2019

Accepted Date: 03-12-2019

Published Date: 03-15-2019

Abstract

Aim: Kidney diseases are common among diabetes mellitus (DM) patients, including diabetic nephropathies (DN) and non-diabetic kidney diseases (NDKD). The clinical differentiation among them is usually not so clear. This study examined kidney biopsies in patients with type-2-DM who underwent native kidney biopsy.

Materials and Methods: We analyzed retrospectively the reported histopathological findings of kidney biopsies obtained from 51 type-2-DM patients who underwent native kidney biopsy in our center between January 2005 and December 2016. Routine processing of kidney biopsies includes evaluation by light microscopy, immunofluorescence and electron microscopy.

Results: There were a total of 51 DM patients, 28 males (54.9%) and 23 females (45.1%). The mean age was 50.8 (47.1-55.2) years, 86% of patients were between 25 and 64 years old. Histological findings showed that 43.1% of patients had diabetic nephropathy. While focal segmental glomerulosclerosis was present in 23.5%- primary in 9.8% and secondary in 13.7%. Lupus nephritis and drug induced interstitial nephritis were each present in 5.8%. MCD and IgA nephropathy were each present in 4%. Lastly membranous nephropathy, diffuse proliferative GN, ANCA associated glomerulonephritis, hypertensive nephrosclerosis and others accounted for 2%.

Conclusion: This is the first study of its kind in Oman covering a period of more than ten years and is representative of the whole country. It showed that the prevalence of NDKD is remarkably frequent in DM patients in whom nephrologists consider kidney biopsy to be an appropriate measure. Among NDKD, FSGS was the most frequent diagnosis.

Keywords: Diabetic Nephropathy, Diabetic Kidney disease, Diabetes mellitus, Sultanate of Oman, Chronic kidney disease, Estimated Glomerular Filtration Rate (e GFR).

INTRODUCTION

Diabetes Mellitus (DM) and chronic kidney disease (CKD) are worldwide public health problems that affect millions of people. The worldwide prevalence of DM is predicted to increase from 2.8% in 2000 to 4.4% in 2030, equivalent to almost 366 million people. The highest growths in prevalence are projected to occur in the Middle East, sub-Saharan Africa, and India [1]. It was estimated that in 2013,382 million people had DM and this is expected to surge to 592 million by 2035 [2]. In addition, in the United States it is anticipated that there would be 165% increase in the prevalence of DM from 2000 to 2050 [3].

DM is a leading cause of CKD worldwide. Nearly 43% of diabetics in the United States have microalbuminuria, a marker of progression to CKD. According to data from National Health and Nutrition Examination Survey (NHANES), diabetic kidney disease (DKD) accounts for 39% of CKD [4]. With the increasing prevalence of CKD, the costs of management are becoming a public health issue. In 2013, more than 30 billion dollars from Medicare expenditure were spent on management of end-stage kidney disease (ESKD), 14 billion of which were due to DKD [4]. Given these factors, clinical societies continue to offer strategies to diagnose and manage DKD to improve outcomes.

The prevalence of DM in Oman is high at around 11.6% [5, 6], a country with a total population of approximately 4.56 million, out of which 2.5million are Omanis [7]. In2000, the age-adjusted prevalence of DM among Omanis aged 30-64 years reached 16.1% compared with 12.2% in 1991, indicating an increasing prevalence [6].

Apart from DN, NDKDs are also common in the diabetic population and these require different treatment and follow-up regimen. The prevalence of NDKD is presumed to exist in between one-sixth and two-thirds of DM patients with overt proteinuria [8-9]. In South Korea, Kim et al. [10] reported 74 cases of kidney biopsy performed in diabetic patients, and nearly half of them had non- diabetic nephropathy. On the other hand, in patients with over 10-year history of type-1 DM, NDKD is a rare clinical condition with a rate of 2-3% [11].

The decision to perform a diagnostic biopsy should be considered very carefully. In patients with type-2 DM, there might be varied time interval between the onset of the disease and the time of the diagnosis; hence the exact duration from the time of onset of diabetes is generally not known. Clinical findings such as proteinuria could be attributed either to different kidney pathology superimposed on DN or be the manifestation of DKD itself. Many clinical features have been considered as predictive factors for NDKD: diabetic nephropathy not associated with diabetic neuropathy or retinopathy [12], hematuria [13], short duration of diabetes [14], deterioration of renal function more rapidly than expected [15], and the presence of acanthocyturia [16] but none of them is 100% sensitive or specific. Differential diagnosis between the various NDKD is important due to the differences in treatment and in clinical outcome regarding kidney function and patients' survival.

The aim of the present study is to evaluate the findings of kidney biopsies performed on patients with type-2 DM with a clinical suspicion of NDKD and to highlight the pathological features other than diabetic nephropathy in the Sultanate of Oman.

Material and Methods

After obtaining approval from the medical ethics and research committee at the Royal Hospital (RH), located in Muscat, Oman, we included in this study 51 patients with type-2 DM who were submitted to a kidney biopsy for clinical suspicion of NDKD from January 2005 to December 2016. The RH has an internationally recognized electronic medical record system called Al Shifaa that uses International Classification of Diseases.

Mohamed et al, had previously described the clinical and laboratory findings of patients with DM that underwent kidney biopsy. In this study, we describe the pathological findings in these patients.

The indications for the kidney biopsy were as follows:

1. Sudden onset of heavy proteinuria
2. Unexplained acute kidney injury
3. Hematuria
4. Proteinuria with no evidence of diabetic retinopathy on fundus examination
5. Other positive immunological or serological findings

like IgA titer above normal, Autoantibodies, C3, C4, etc.

All kidney biopsy specimens were obtained via percutaneous needle biopsy according to Royal hospital – Nephrology and Renal Transplant Department Guidelines for Percutaneous Kidney Biopsy, which was approved earlier by Royal Hospital Policy Committee.

All kidney biopsies were submitted for light microscopic (LM), immunofluorescence (IF) and electron microscopy (EM) examination. For LM, the sample was fixed with neutral buffered formalin and processed overnight followed by paraffin embedding. Blocks were serially sectioned at 3micron thickness and were stained with hematoxylin and eosin (H&E) stain, Periodic-acid Schiff (PAS) and Jones' silver stain to evaluate glomerular basement membranes (GBM). Scarring was assessed using Masson trichrome stain. Majority of cases were also stained with congo red stain to exclude amyloidosis. All compartments of the kidney were evaluated (glomeruli, tubules, interstitium and blood vessels) for injury, inflammation, scarring or accumulation of abnormal materials. The standard immunofluorescence panel was applied to all cases namely: IgA, IgG, IgM, C3, C1q, kappa light chain, lambda light chains and fibrinogen. The presence of each of these was assessed individually by the direct immunofluorescence (IF) technique on frozen sections.

For EM examination, tissue was processed and then embedded in resin blocks. Toluidine blue-stained 1-um thick semi-thin sections were used to assess for presence of glomeruli, any structural changes including mesnagial or endocapillary hypercellularity, segmental sclerosis or crescents. Representative 1 to 2 glomeruli were selected for further processing for ultrastructural examination. The features evaluated included the thickness and texture of the glomerular basement membranes, the appearance of the podocytes and extent of foot process effacement divided into either focal or diffuse. Focal was defined as area of foot process effacement involving less than 50% of the surface area of the glomerular basement membranes, whereas diffuse was defined as more than 50% of surface area showing effacement. The presence of subendothelial, subepithelial or intramembranous deposits was noted. The appearance of the endothelial cells, presence of subendothelial lucencies, and glomerular basement membrane duplication with mesangial cell interpositioning was also recorded. Mesangial areas were assessed for increase in cells and matrix and presence of any deposits. Careful examination for presence of organized deposits, particularly amyloid and for any abnormal intracellular accumulations was also performed.
Biopsies were regarded as adequate if they contained at least ten glomeruli for light microscopy and at least one glomerulus each for immunofluorescence and electron microscopy.
Diabetic nephropathy was defined as findings of mesangial expansion, diffuse intercapillary glomerulosclerosis and/or Kimmelstiel-Wilson nodule formation, GBM thickening, presence of fibrin cap, or capsular drops.
The data entry was rechecked by 2 researchers. Statistical analysis was done using Stata software (Chicago, Ill.).
Descriptive statistics were used to present the distribution of the histological types of glomerulonephritis and their relative frequencies. Data were described as frequencies and percentages for categorical variables. Continuous variables were reported as median and ranges or as mean and standard deviations. A p-value equal to or less than 0.05 was considered to be significant.

Results

During the period from January 2005 to end of December 2016, a total of 51 diabetic patients, 28 (54.9%) males and 23 (45.1%) females underwent a renal biopsy in the Royal Hospital.

Based on pathological findings, table 1 highlights the histopathological findings by LM. An adequate number of glomeruli was present in 62.7% of biopsies. The most common glomerular findings were the presence of glomerular mesnagial matrix expansion in 75.5%, glomerular sclerosis in 43.1%, and19.6% of cases showed endocapillary hypercellularity, while only 7.7 % of cases had crescents. Interstitial fibrosiswas presentin 76.5%and tubular atrophy and arteriolar hyalinosis was 72.5% for each.

Immunofluorescence examination was available for all biopsies. 54.8% of cases had some positive staining with IF, the most common being IgM in 11.7%, followed by C3 and C1q in 9.8%, IgG was positive in 5.9% and IgA in 4%,

there was no light chain restriction by kappa and lambda in any of our biopsies.

Table 1: Histopathological Findings by Light Microscopy

Variant	Frequency	Percent
Glomerular Number		
Adequate =10	**32**	**62.7**
Inadequate<10	**19**	**37.3**
Obsolete Glomeruli		
No	**17**	**33.3**
Yes	**34**	**66.7**
Sclerosed Glomeruli		
N0	**29**	**56.9**
Yes	**22**	**43.1**
Cellular Crescents		
No	**50**	**98.1**
Yes	**1**	**1.9**
Fibrous Crescents		
No	**50**	**98.1**
Yes	**1**	**1.9**
Fibro Cellular Crescents		
No	**49**	**96.1**
Yes	**2**	**3.9**
Glomerular Matrix Expansion		
No	**13**	**25.5**
Yes	**38**	**74.5**
Endocapillary Proliferation		
No	**41**	**80.4**
Yes	**10**	**19.6**
Capillary Wall Pathology		
No	**32**	**62.8**
Yes	**19**	**37.2**
Tubular Atrophy		
No	**14**	**27.5**
Yes	**37**	**72.5**
Tubulitis		
No	**42**	**82.4**
Yes	**9**	**17.6**
Interstitial Atrophy		
No	**12**	**23.5**
Yes	**39**	**76.5**
Arterial Hyalinosis		
No	**14**	**27.5**
Yes	**37**	**72.5**

Table 2 shows histopathological findings by EM. Foot process fusion was present in 96%, GBM thickening in 76% and mesangial expansion by matrix in 80%.There were no organized deposits in any of our cases.

Table 2: Histopathological Findings by Electron Microscopy

Variant	Frequency	Percent
Glomerular Number		
Adequate =1	**25**	**100**
Inadequate<1	**0**	**0**
Foot Process fusion		
No	**1**	**4**
Yes	**24**	**96**
Glomerular Basement Membrane Thickness Abnormalities		
No	**6**	**24**
Yes	**19**	**76**
Sub endothelial deposit Abnormalities		
No	**23**	**92**
Yes	**2**	**8**
Epithelial and Subepthelial Abnormalities		
No	**22**	**88**
Yes	**3**	**12**
Lipid Vacuoles		
No	**22**	**88**
Yes	**3**	**12**
Mesangial Expansion		
No	**5**	**20**
Yes	**20**	**80**
Mesangial Deposit		
No	**19**	**76**
Yes	**6**	**24**

Based on light microscopy, immunofluorescence and electron microscopy findings, 43.1% of patients had diabetic nephropathy only with no additional pathology, whereas 56.9% of patients had some form of NDKD. The most common NDKD was focal segmental glomerulosclerosis in 23.5% of biopsies with primary FSGS being favored in 9.8% and secondary in 13.7%.Lupus nephritis and drug induced interstitial nephritis were each present in 5.8% of biopsies. 4% of patients had IgA nephropathy defined as dominant mesangial and/or capillary wall staining with IgA antibody. Also, minimal change disease (MCD) was diagnosed in 4% of our biopsies. Lastly membranous nephropathy, diffuse proliferative glomerulonephritis (GN), ANCA associated GN and hypertensive nephropathy were each present in 2% of our biopsies (table 3).

Table 3: Final Histopathological Diagnosis.

Diagnosis	Frequency	Percent
1ry FSGS	**5**	**9.8**
2ry FSGS	**7**	**13.7**
Minimal Change Disease	**2**	**4**
Membranous GN	**1**	**2**
IgA Nephropathy	**2**	**4**
Lupus GN	**3**	**5.8**
Diffuse Proliferative Gn	**1**	**2**
Diabetic GN	**22**	**43.1**
ANCA	**1**	**2**
HTN Nephropathy	**1**	**2**
Drug Induced	**3**	**5.8**
Others	**3**	**5.8**

There was no statistically significant difference between clinical diagnostic impression before biopsy and final pathological diagnosis. Table 4 shows the frequencies of clinical diagnostic impression. FSGS, especially secondary, was underestimated by the clinicians being suspected in 9.8% of cases whereas it was histopathologically identified in 23.5% of cases. IgA nephropathy was not suspected clinically in any of the cases but was diagnosed in 4% of biopsies. Drug inducing nephritis and lupus nephritis, were underestimated clinically in 2% of patients but accounted for 5.8% each on final histopathological diagnosis. While, crescentic GN was overestimated by clinical judgment compared to biopsy finding (5.8% vs 0%).Same for ATN, was entertained clinically in 9.8% but was not present in any of the biopsies.

Table 4: The Frequencies of Clinical Diagnostic Impression.

Variant	Frequency	Percent
Primary FSGS	**4**	**7.8**
Secondary FSGS	**1**	**2**
Minimal GN	**2**	**4**
Membranous GN	**1**	**2**
Lupus GN	**1**	**2**
Diffuse PGN	**1**	**2**
Cresentic GN	**3**	**5.8**
Diabetic GN	**18**	**35.2**
ATN	**5**	**9.8**
ANCA	**1**	**2**
Drug Induced GN	**1**	**2**
Others	**13**	**25.4**

Clinical judgment and histopathological diagnosis came in agreement for minimal change disease, membranous GN and ANCA associated GN.

Discussion

This study describes the pathological findings of patients with type II DM who underwent native kidney biopsy at Royal hospital, Sultanate of Oman in the period from 2005 to 2016. Almost 45% of patients had diabetic nephropathy histologically. However, focal segmental glomerulosclerosis was present in 23.5%, lupus nephritis and drug induced interstitial nephritis were present in 5.8%. MCD and IgA nephropathy were each present in about 4% of the biopsies. Lastly membranous nephropathy, diffuse proliferative GN, ANCA associated GN, hypertensive nephropathy and others

were each present in 2% of the biopsies. In addition, there was no statistically significant difference between clinical diagnostic impression before biopsy and the final pathological diagnosis.

Diabetic nephropathy (DN) is the leading cause of ESKD world-wide [17]. Projections from the recent Indian Council of Medical Research–India Diabetes study has shown that India has 62.4 million people with DM making DN an important cause of CKD [18]. Studies from India and rest of Asia showed a high prevalence of DN as a cause of CKD [19-20]. The progressive rise in the number of patients with ESKD due to DN is a major social and economic problem in several countries. Furthermore, prognosis in such patients is poor compared to patients with ESKD due to other kidney diseases and hence special treatment guidelines are defined for this subset [21]. Proteinuria in DM patients is usually interpreted as a clinical manifestation of DN [22]. Although the renal biopsy is regarded as the gold standard method of evaluating proteinuria patients, it is rarely used in subjects with DM with isolated proteinuria [23] and the primary aim of the kidney biopsy in proteinuric patients with DM is to confirm and or exclude NDKD.

Worldwide, DN is the leading cause of ESKD, with a reported frequency of 10-15% in T2DM patients, however there is a great discrepancy between countries. In retrospective series of DM patients, NDKD was found in between 7-44% in accordance with patient selection criteria [24-25]. In different studies, the prevalence of NDKDs was reported as 22% in Caucasians. An Asian study reported that NDKD occurred in 26.7% [26]. A European study from Denmark reported it as 3% [13], whereas another study from Italy reported it to occur in 12% [27].

The indications for doing kidney biopsy in diabetic patients with CKD are; recently diagnosed DM within < 3 months in patients with CKD (52.9%), proteinuria with lack of diabetic retinopathy (37.8%), microscopic hematuria (77.1%) and positive immunological findings like high IgA, low C3/C4, positive ANA and ANCA (Mohammed et.al SJKDT).

A study from Iran, revealed that indications for biopsies in diabetic patients were as follows: unexplained rapidly increasing proteinuria (67.5%), unexpected serum creatinine (2.2%), active urine sediment and rising serum creatinine (8.7%), proteinuria and rising serum creatinine (19.7%), and all of them (2.2%). Urine sediment was active in (17.4%) patients. Nephrotic range proteinuria was observed in (58.7%) subjects [28].

Adequate glomerular number is important which reflects proper pathological diagnosis. In our study an adequate glomerular samplewas present in 62.7% of tissue submitted for LM and 100% of tissue submitted for both IF and EM.

An increase in GBM thickness leads to hematuria in 33% of patients with typical diabetic glomerulosclerosis [29].In our study GBM thickening was there in 76% of all biopsies while foot process fusion was there in 96%.

In our study, we found 44.9% incidence of DN. These patients all had pathologic hallmarks of DN, including increased thickness of GBM and mesangial expansion. According to the new classification of glomerular lesions in DN, the degree from light to severe are presented as follows [29]:

I. Mild or nonspecific light microscopy changes and electron microscopy-proven glomerular
basement membrane thickening.

II-a. Mild Mesangial expansion.

II-b. Severe Mesangial expansion.

III. Nodular sclerosis (Kimmelstiel-Wilson lesion).

IV. Advanced diabetic glomerulosclerosis

In our study, most patients' glomerular lesions in DN were I, IIa or IIb. This reflects the clinical status of early diabetic patients being biopsied because of NDKD clinical features presentations, whereas diabetic patients with advanced disease were hardly biopsied and hence later stages were not found among our biopsy series.

By IF examination, positive staining was present in 54.8 % of all biopsies, indicating other findings other than DN. IgA positive stain was there in 2 biopsies (4.1%), IgM in 6 biopsies 11.7%, IgG in 3 biopsies (5.9%), and C3 in 5 biopsies (9.8%), C1q in another 5 biopsies (9.8%). Many biopsies showed a combination of positive staining; however interpretation was based on the pattern and intensity of staining.

In our study, histopathological findings support-

ing diabetic nephropathy were present in (43.1%) of all biopsies, while pathological findings other than diabetic nephropathy were present in 56.9% mainly with FSGS in (23.5%), lupus nephritis and drugs induce GN ,5.8% for each and IgA nephropathy in 4%. A study from Pakistan by Muhammad Arif et al [30], revealed that minimal change disease (MCD) and/or focal segmental glomerulosclerosis (FSGS) were the most common NDKD. These results are similar to a study conducted in USA, which reported FSGS (21%) to be the most common lesion in patients with type-II diabetes followed by MCD (15.3%) [31]. Ghani AA et al [32], a study from Saudi Arabia, revealed that NDKD was detected in 45.8% of biopsies of diabetic patients. This was in concordance with previous studies where the prevalence of NDKD was found to range from 45% to 57% [33- 34]. Kittrawee Kritmetapak et al [35], Thailand, revealed that 49% of type 2 diabetes patients who underwent renal biopsy had NDKD, either isolated or superimposed on underlying DN. In another study from Taiwan, AIN was the most prevalent NDKD (46.5%), followed by membranous nephropathy and IgA nephropathy [14]. An Indian study found AIN to be the most common NDKD found in 18% of the patients with mixed renal disease (NDKD superimposed on DN), while membranous nephropathy (19.2%) was the most frequent diagnosis in patients with isolated NDKD [36]. IgA nephropathy is reported to be the most frequent type of NDKD in Chinese, Korean and Japanese population with diabetes [37, 38 and 39]. Keeping in mind that IgA nephropathy is the most common primary glomerulonephritis in the general population of these countries, with a prevalence of 28.3% to 50.6% [40].

In our study, comparing the clinical impression prior to biopsy with the final histopathological diagnosis showed that DN was underestimated clinically being suspected in 35.2% of cases but turned out to be the main diagnosis in 43.1%. On the other hand, the clinical impression of NDKD was entertained in 64.8%, but was present in 56.9% based on biopsy findings. FSGS was the clinical suspicion in 9.8% (7.8% presumed primary and 2% presumed secondary) but was diagnosed in 23.5% (9.8% primary and 13.7% secondary). IgA nephropathy was not the primary suspicion in any of the cases but was in the final diagnosis in 4%. Similarly lupus nephritis and drug induced GN, were suspected clinically in 2% of cases and this increased to 5.8% for each in the final diagnosis. While in the case of MCD the clinical impression and the final pathological diagnosis were very similar at 4% and 4%, same as for membranous nephropathy, diffuse proliferative GN and ANCA at 2% for each. However there was a striking difference between the clinical impression and the final diagnosis in the case of ATN and crescentic GN, which were suspected clinically in 9.8% and 5.8% of biopsies, respectively, yet both of them were not there in the final biopsy diagnosis.

The high prevalence of NDKD in our study (56.9%) supports the ongoing call for more consideration to biopsy diabetic patients presenting with the criteria stated above, as the finding of NDKD requires a different therapeutic approach (other than or in addition to conventional angiotensin-converting enzyme inhibitors or angiotensin receptor blockers) as steroids and other immunosuppressive medications. New therapeutic agents for the treatment of DN have recently been characterized. Endothelin receptor antagonists, sodium-glucose co-transporter 2 inhibitors and agents targeting inflammation/fibrosis are probably the most promising candidates on top of the classical RAAS blockers [41, 42]. Therefore, it is mandatory that patients with diabetic kidney disease are adequately classified, differentiating clearly those with DN and those with NDKD. In addition, among those with DN, a reliable classification within different pathological categories [43, 44] will be of great value to individualize treatment strategies.

Conclusion

The present findings show that NDKD are a very common clinical condition in type-2 DM patients. The differential diagnosis of DNs and NDKDs is of considerable important because of their management approach and prognosis.

In Oman, among diabetic patients, pathological findings other than diabetic nephropathy were present in 56.9% mainly with FSGS in (23.5%), lupus nephritis in 5.8% and IgA nephropathy in 4% whereas diabetic nephropathy was the main finding in (43.1%) of all biopsies.

Therefore, there is a great need for more consideration to biopsy diabetic patients, as the finding of NDKD requires a different therapeutic approach. This, hopefully, will help to manage these patients better and therefore, ameliorate

the progression to end stage kidney disease over time and therefore delay the need for RRT.

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