

Diabetic Nephropathy among Adult Patients with Type 2 Diabetes Mellitus in Saudi Arabia

Ahmed Dakhel Alrehaili¹, Khaled Mohammed Almuraydhi², Mustafa Taher Ali AL Essa³,
Abdullah Mohammed A Aljabir⁴, Yaser Yousef Khogheer⁵, Mohammed Walid Adham⁶,
Musaab Mohammad A. Alshanqeeti⁷, Ibrahim Mohammed I Eid⁸, Sultan Ahmed M. Alburayk⁹,
Mohammed Alean Albalawi¹⁰, Moath Mohammad Alothman¹¹, Ahmad Abdullah Algarni¹²

1-King Faisal University, 2- King Fahad Hospital Alhofof , 3-Prince Saud Bin Jalawy Hospital (Al Ahsa) ,
4- Khamis Mushit Ben Sina PHC , 5- East Jeddah Hospital , 6- King Fahad Hospital Jeddah , 7- Umm
Alquraa University , 8- King Saud Bin Abdulaziz University for Health Sciences , 9- King Salman Hospital,
Saudi Arabia, Riyadh , 10- Madinah PHC ,11- PHC at Dammam City, 12- King Abdulaziz Hospital

ABSTRACT

Background: the occurrences of diabetes mellitus and diabetic nephropathy have increased quickly in the past few decades and have become an economic burden to the healthcare system in KSA. Diabetic nephropathy is a major complication of diabetes mellitus and is a primary cause of end-stage renal disease (ESRD). The occurrence of non-diabetic renal disease (NDRD) in diabetic patients has been increasingly recognized in recent years. It is generally believed that it is difficult to reverse diabetic nephropathy, whereas some cases of non-diabetic renal disease are readily treatable and remittable. However, diabetic nephropathy is known to co-exist with non-diabetic renal disease in a poorly defined population of patients with type 2 diabetes mellitus. This study estimated the pervasiveness of co-existing diabetic nephropathy and non-diabetic renal disease in Saudi patients.

Methods: data were retrospectively analyzed from 122 patients with type 2 diabetes mellitus who had experienced a renal biopsy between February 2014 and June 2017 at King Abdulaziz Hospital, region(s), KSA. Male patients numbered 75 (61.5%) of the study population. The biopsies were performed as urinary abnormalities or renal functions were atypical of a diagnosis of diabetic nephropathy. Biopsy samples were examined using light, immunofluorescence (IF) and electron microscopy (EM). Clinical parameters were recorded for each patient at the time of biopsy.

Results: nineteen of 122 diabetic patients (8%) had co-existing diabetic nephropathy and non-diabetic renal disease. These patients showed clinical features and pathologic characteristics of diabetic nephropathy, containing a high prevalence of diabetic retinopathy (88.8%), a long duration of diabetes, increased thickness of the glomerular basement membrane (GBM) and mesangial expansion. Nonetheless, they similarly presented with clinical findings which were inconsistent with diabetic nephropathy, such as hematuria, rapidly progressive renal failure and marked proteinuria. Immunoglobulin A (IgA) nephropathy was apparent in 5 out of the 10 patients (50%), tubulointerstitial lesions were found in two patients (20%), membranoproliferative glomerulonephritis (MPGN) in two patients (20%) and membranous nephropathy (MN) in one patients (10%).

Conclusion: retrospective analysis of biopsy data suggests that approximately 8% of Saudi patients with type 2 diabetes mellitus may have co-existing diabetic nephropathy and non-diabetic renal disease. The most common histological diagnosis in our small series was IgA nephropathy.

Keywords: Diabetic nephropathy, Renal histopathology, Non-diabetic renal disease, Renal biopsy, Diabetes mellitus.

INTRODUCTION

The occurrence of diabetes mellitus (DM) and diabetic nephropathy (DN) have increased quickly in the past few decades and have become an economic burden to the healthcare system in KSA. Diabetic nephropathy, also known as diabetic glomerulosclerosis or diabetic kidney disease, is a major complication of DM and is a leading cause of end-stage renal disease (ESRD). Persistent and slowly progressive proteinuria is a characteristic of DN and diabetic renal failure⁽¹⁻³⁾. The diagnosis of diabetic nephropathy is regularly inferred in cases where renal biopsy has not produced definitive

outcomes. These are regularly patients with a 7 to 10-year history of type I DM, who have demonstrable diabetic retinopathy and a history of microalbuminuria. These patients present no indication of a sudden start of marked proteinuria, abnormal kidney size, hematuria, or other renal disease^[4, 5]. Renal biopsy in this setting will not be diagnostically useful, whereas it will be inferred as diabetic nephropathy⁽³⁾. Most of our knowledge regarding the nature of kidney illness in patients with type 2 diabetes mellitus (T2DM) is derived from studies of patients with type I diabetes mellitus^[1]. Nonetheless, biopsy data from patients with type

2 diabetes mellitus with renal disease or proteinuria present that these patients have a more heterogeneous group of renal lesions than patients with type I diabetes mellitus^[6, 7]. Based on these results the incidence of non-diabetic renal disease (NDRD) in diabetic patients has been increasingly acknowledged in recent years. Nonetheless, the pervasiveness of non-diabetic renal disease differs extensively in different areas of the world and is stated to range from 15.7% to 82.9%^[8-17]. The current retrospective, single center, analysis was undertaken to evaluate the pervasiveness of DN complicating non-diabetic renal disease in Saudi patients with type 2 diabetes mellitus. The pathogenic mechanism of DN that complicates non-diabetic renal disease is thought to be different to the mechanisms that underlie either DN or non-diabetic renal disease alone. We consequently studied the correlations between the clinical and pathologic features in these patients.

METHODS

The study included data from 122 patients with type 2 diabetes mellitus who experienced renal biopsy between February 2014 and June 2017 at King Abdulaziz Hospital, region(s) KSA. Male patients numbered 75 (61.5%) of the study population. Patients with known DN were excluded from the study as renal biopsy was not regularly performed in these patients at this institution. Patients with present acute ailment comprising infectious disease were correspondingly excluded from entry. The existence of immunologic diseases, infections and malignancy was similarly examined prior to inclusion into the study. Diabetes mellitus was diagnosed utilizing the criteria of the American Diabetes Association^[18]. The clinical and demographic parameters were noted for every patient at the time of renal biopsy. These parameters comprised period of diabetes, electrocardiogram, blood pressure, echocardiogram, kidney ultrasound and fundoscopic findings. Laboratory studies comprised fasting blood sugar, urinalysis, glucose tolerance test, blood urea nitrogen, albumin, glycated hemoglobin (HbA1c), urine osmotic pressure, 24-hour protein excretion, total protein, serum creatinine levels and creatinine clearance. Nephrotic syndrome was defined as proteinuria (>3.5 g/day) accompanied by edema, hyperlipidemia, hypoproteinemia, or other metabolic disorders^[19]. Nephritic syndrome was defined as pathologically diffuse inflammatory changes in the glomeruli accompanied by hematuria with red blood cell casts, mild proteinuria, and, regularly, hypertension, edema and azotemia. Renal failure was diagnosed in patients with blood urea nitrogen >20 mg/dl and

serum creatinine >1.4 mg/dl. Hypertension was defined as a systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg.

In all cases renal biopsy was performed as urinary abnormalities or renal function was varying with the clinical expression or the natural history of DN. Percutaneous renal biopsy was performed as designated by Veiga^[20]. Renal tissue submitted for diagnosis was divided into three portions. One portion was fixed in buffered formalin and processed onto paraffin blocks for light microscopy examination. Sections were stained with hematoxyline and eosin, periodic acid-Schiff (PAS), silver methanamine and Masson's trichrome. The second portion of tissue was frozen for direct immunofluorescence (IF) studies using fluorescein isothiocyanate (FITC) conjugated antibodies for immunoglobulin A (IgA), immunoglobulin G (IgG), immunoglobulin M (IgM), C3, C1q and fibrinogen (FIB). The third tissue portion was fixed in Trump's electron microscopy (EM) fixative and processed into resin blocks. Ultrathin sections were stained with uranyl acetate and lead citrate, and examined using a transmission electron microscope.

Statistical analysis was performed using SPSS version 17.0 for Windows (IBM SPSS Statistics, Armonk, NY, USA). Data were expressed as mean \pm SD. The Spearman rank correlation test was used to determine the associations between clinical parameters and histopathological findings. Values of $P < 0.05$ were considered statistically significant. **The study was done according to the ethical board of King Abdulaziz university.**

RESULTS

Data were retrospectively analyzed from 122 patients with T2DM. Male patients numbered 75 (61.5%) of the study population. There were 10 cases (8.2%) with a pathologic diagnosis of DN, 102 cases (83.6%) with NDRD and 10 cases (8.2%) had DN complicating NDRD. The proportion of males was 64% in DN, 59% in NDRD and 89% in DN complicating non-diabetic renal disease, respectively. The clinical features and laboratory data are summarized in Table 1. The population included 9 men and one woman between 30 and 62 years of age, with only one patient older than 60 years. All patients had T2DM; the period of diabetes at the time of renal biopsy ranged from 2 to 15 years. Diabetic retinopathy was present in 9 patients and the majority of patients had hematuria (8 cases, 88.8%). Eight patients had hypertension, two patients had nephrotic syndrome, three patients had nephritic syndrome and five patients had renal dysfunction.

Table 1: The clinical data of diabetic nephropathy (DN) with non-diabetic renal disease (NDRD) in patients with type 2 diabetes mellitus (T2DM)

Case	Age (years) / sex	Duration of T2DM (years)	Diabetic retinopathy	Fasting blood sugar (mmol/l)	HbA1c (%)	Clinical manifestations	Hematuria	Urinary protein (g/day)	BUN (mg/dl)	Serum creatinine (mg/dl)	History of hypertension
1	39/M	11	+	7,8	7.0	CRF	2+	3,8	23,1	1,5	+
2	30/M	5	+	9.0	7,8	NG	+	1,4	13,4	0.6	-
3	57/M	15	+	7,9	6,4	NG	2+	5,5	17,8	1,2	+
4	47/F	14	+	8,7	4,8	CRF	2+	4,9	21,6	1,4	+
5	45/M	8	+	10,5	8,6	NS	2+	3.0	18,9	1.0	+
6	47/M	6	+	5,2	6	NS	+	7,1	17,2	0.9	-
7	62/M	9	+	4,4	7,5	ARF	+	7.0	21,5	3,4	+
8	56/M	3	+	5,1	5,1	ARF	-	1,8	40.2	2,9	+
9	46/M	15	+	19,1	11,4	CRF	2+	3,3	22,2	1,4	+
10	51/M	5	-	5,2	5,7	NG	3+	6,7	42.5	1,3	+

Patients with a longer history of diabetes had higher urinary protein levels than those with a shorter duration of diabetes ($r = 0.69$, $P < 0.05$). Nonetheless, there was a poor correlation between disease period and fasting blood sugar ($r = 0.126$, $P > 0.05$) and HbA1c ($r = 0.256$, $P > 0.05$).

Renal pathology findings are summarized in Table 2. All patients had diabetic renal lesions complicated with NDRD. The most common NDRD finding was IgA nephropathy, which was present in 5 patients (50%). Two patients had tubulointerstitial lesions, two patients had membranoproliferative glomerulonephritis (MPGN) and one patient had membranous nephropathy (MN).

Table 2: The histology of diabetic nephropathy (DN) with non-diabetic renal disease (NDRD)

Case	IgA	IgM	IgG	C3	C1q	FIB	Diabetic renal lesion	NDRD
1	2+	2+	2+	+	±	-	Diffuse and nodular glomerulosclerosis	IgA nephropathy
2	-	2+	-	3+	+	-	Diffuse and nodular glomerulosclerosis	Tubulointerstitial lesion
3	2+	+	+	±	-	2+	Diffuse and nodular glomerulosclerosis	IgA nephropathy
4	2+	±	+	3+	-	2+	Diffuse and nodular glomerulosclerosis	IgA nephropathy
5	±	3+	2+	3+	2+	-	Diffuse and nodular glomerulosclerosis	Membranous nephropathy
6	2+	2+	+	2+	-	-	Diffuse glomerulosclerosis	IgA nephropathy
7	2+	2+	3+	-	±	-	Diffuse and nodular glomerulosclerosis	Membranoproliferative glomerulonephritis
8	3+	+	2+	2+	-	2+	Diffuse glomerulosclerosis	IgA nephropathy
9	±	+	-	-	-	-	Diffuse glomerulosclerosis	Membranoproliferative glomerulonephritis
10	-	3+	3+	2+	-	2+	Diffuse and nodular glomerulosclerosis	Tubulointerstitial lesion

DISCUSSION

The incidence of non-diabetic renal disease in diabetic patients is well acknowledged. A variety of renal lesions may arise in diabetic patients, for instance, IgA nephropathy, membranous nephropathy, mesangial proliferative glomerulonephritis, hypertensive renal disease and focal segmental glomerular sclerosis. In some diabetic patients, diabetic nephropathy is complicated by co-existing NDRD. We summarize the relevant studies [4,8,9,10,11,17, 21-23], which showed that glomerular disease (58.2%) residues the most common renal complication in diabetic patients with co-existing DN and NDRD. The review presented that the three most common forms of glomerular disease were IgA nephropathy (14.1%), mesangial proliferative glomerulonephritis (10%) and post-infectious glomerulonephritis (10%). Tubulointerstitial lesions (25.5%) and vascular lesions (10%) similarly existed in such patients. In the current study, we found a high frequency of DN complicating NDRD (8.2%). These patients all had pathologic hallmarks of diabetic nephropathy, containing increased thickness of the glomerular basement membrane (GBM) and mesangial expansion. Consistent with the new classes of glomerular lesions in diabetic nephropathy, the degree from light to severe are presented as follows: I. Mild or nonspecific light microscopy changes and electron microscopy-proven glomerular basement membrane thickening. IIa. Mild mesangial expansion. IIb. Severe mesangial expansion. III. Nodular sclerosis (Kimmelstiel-Wilson lesion). IV. Advanced diabetic glomerulosclerosis [24,25]. In our study, most patients' glomerular lesions in diabetic nephropathy were IIb or III.

The most common NDRD in our patients was IgA nephropathy, which accounted for 50% of all cases, followed by tubulointerstitial lesion (20%) and MPGN (20%). The high pervasiveness of IgA nephropathy was in accordance with findings from the aforementioned literature review, which presented pervasiveness rates ranging from 7% to 45% [8,10,21,22]. The disease spectrum of DN complicating NDRD in KSA might be thought to be different from that in other parts of the world. There was a high pervasiveness of diabetic retinopathy among our 10 cases of co-existing DN and NDRD. The mean period of diabetes was more than 8 years, and there was a direct relationship between period of diabetes and the severity of proteinuria. The poor correlation between disease period, fasting blood sugar and HbA1c does not essentially designate that DN is the only factor affecting disease progression, since

the poor correlation coefficients may have been the consequence of the diversity of other types of NDRD. It is possible, nonetheless, that is in the small populace. The other unexpected result of the current study was the high incidence of hypertension (8 cases, 80%), especially as some workers report absence of hypertension in diabetes mellitus as one of the differential diagnostic features of NDRD [21]. These results designate that blood pressure control is of primary significance in the avoidance of progressive renal disease.

Our results specify that there are different clinical and pathologic features in diabetic patients with diabetic nephropathy complicating non-diabetic renal disease. These patients have some of the clinical and pathologic features of diabetic nephropathy, which comprise a high pervasiveness of diabetic retinopathy, a long duration of diabetes, increased thickness of the GBM and mesangial expansion. Other clinical findings are varying with the natural history of diabetic nephropathy, comprising the incidence of hematuria, quickly progressive renal failure and severe proteinuria. These various clinical manifestations might be the direct importance of a different pathologic diagnosis within the populace. IgA nephropathy was the most common histological diagnosis in patients undergoing renal biopsy. Nevertheless, the pathologic types of NDRD in diabetic nephropathy complicating non-diabetic renal disease in diabetic patients are no different to those in non-diabetic patients in previous studies.

CONCLUSION

In the current study, retrospective analysis of biopsy data concluded that almost 8% of Saudi patients with type 2 diabetes mellitus may have co-existing diabetic nephropathy and non-diabetic renal disease. The most common histological diagnosis in our small series was IgA nephropathy. Nonetheless, it is single-center study with a small number of patients. Larger, multicenter randomized prospective studies are, consequently, required to confirm these preliminary findings.

REFERENCES

1. **Kramer HJ, Nguyen QD, Curhan G, Hsu CY (2003):** Renal insufficiency in the absence of albuminuria and retinopathy among adults with type 2 diabetes mellitus. *JAMA.*, 289(24):3273–3277.
2. **Spijkerman AM, Dekker JM, Nijpels G, Adriaanse MC, Kostense PJ, Ruwaard D, Stehouwer CD, Bouter LM, Heine RJ (2003):** Microvascular complications at time of diagnosis of type 2 diabetes are similar among diabetic patients detected by targeted screening and patients newly diagnosed in general

- practice: the hoorn screening study. *Diabetes Care*,26(9):2604–2608.
3. **Suzuki Y, Ueno M, Hayashi H, Nishi S, Satou H, Karasawa R, Inn H, Suzuki S, Maruyama Y, Arakawa M (1994):** A light microscopic study of glomerulosclerosis in Japanese patients with noninsulin-dependent diabetes mellitus: the relationship between clinical and histological features. *Clin Nephrol.*,42(3):155–162.
 4. **Lin YL, Peng SJ, Ferng SH, Tzen CY, Yang CS (2009):** Clinical indicators which necessitate renal biopsy in type 2 diabetes mellitus patients with renal disease. *Int J Clin Pract.* ,63(8):1167–1176.
 5. **Mak SK, Gwi E, Chan KW, Wong PN, Lo KY, Lee KF, Wong AK (1997):**Clinical predictors of non-diabetic renal disease in patients with non-insulin dependent diabetes mellitus. *Nephrol Dial Transplant.*,12(12):2588–2591.
 6. **Tone A, Shikata K, Matsuda M, Usui H, Okada S, Ogawa D, Wada J, Makino H(2005):** Clinical features of non-diabetic renal diseases in patients with type 2 diabetes. *Diabetes Res Clin Pract.*,69(3):237–242.
 7. **Mauer SM, Chavers BM, Steffes MW (1990):**Should there be an expanded role for kidney biopsy in the management of patients with type I diabetes? *Am J Kidney Dis.*,16(2):96–100.
 8. **Chang TI, Park JT, Kim JK, Kim SJ, Oh HJ, Yoo DE, Han SH, Yoo TH, Kang SW(2011):** Renal outcomes in patients with type 2 diabetes with or without coexisting non-diabetic renal disease. *Diabetes Res Clin Pract.* ,92(2):198–204.
 9. **Soni SS, Gowrishankar S, Kishan AG, Raman A(2006):** Non diabetic renal disease in type 2 diabetes mellitus. *Nephrology (Carlton)* ,11(6):533–537.
 10. **Ghani AA, Al Waheeb S, Al Sahow A, Hussain N(2009):** Renal biopsy in patients with type 2 diabetes mellitus: indications and nature of the lesions. *Ann Saudi Med.* ,29(6):450–453.
 11. **Huang F, Yang Q, Chen L, Tang S, Liu W, Yu X (2007):**Renal pathological change in patients with type 2 diabetes is not always diabetic nephropathy: a report of 52 cases. *Clin Nephrol.*,67(5):293–297.
 12. **Zhuo L, Ren W, Li W, Zou G, Lu J (2013):** Evaluation of renal biopsies in type 2 diabetic patients with kidney disease: a clinicopathological study of 216 cases. *Int Urol Nephrol.* ,45(1):173–179.
 13. **Chawarnkul O, Vareesangthip K, Ongajyooth L, Cheunsuchon B, Parichatikanond P(2009):** Non-diabetic glomerular disease in type II DM: 10 years' experience. *J Med Assoc Thai.* ,92(2):S57–S60.
 14. **Hashim Al-Saedi AJ(2009):** Pathology of nondiabetic glomerular disease among adult Iraqi patients from a single center. *Saudi J Kidney Dis Transpl.*,20(5):858–861.
 15. **Zukowska-Szczechowska E, Tomaszewski M(2004):** Renal affection in patients with diabetes mellitus is not always caused by diabetic nephropathy. *Rocz Akad Med Bialymst.* ,49:185–189.
 16. **Yaqub S, Kashif W, Hussain SA(2012):** Non-diabetic renal disease in patients with type-2 diabetes mellitus. *Saudi J Kidney Dis Transpl.* ,23(5):1000–1007.
 17. **Nzerue CM, Hewan-Lowe K, Harvey P, Mohammed D, Furlong B, Oster R(2000):** Prevalence of non-diabetic renal disease among African-American patients with type II diabetes mellitus. *Scand J Urol Nephrol.* ,34(5):331–335.
 18. **American Diabetes Association(2007):** Diagnosis and classification of diabetes mellitus. *Diabetes Care*,30(1):S42–S47.
 19. **Barry M(2007):** The Kidney. <https://archive.org/.../BrennerAndRectorsTheKidney/BrennerAndRectorsTheKidney>
 20. **Veiga PA, Moxey-Mims MM, Springate JE, Feld LG(1991):** A simple method for percutaneous renal biopsy. *Child Nephrol Urol.*,11(4):196–198.
 21. **Hironaka K, Makino H, Ikeda S, Haramoto T, Ota Z(1991):** Nondiabetic renal disease complicating diabetic nephropathy. *J Diabet Complications*,5(2–3):148–149.
 22. **Pham TT, Sim JJ, Kujubu DA, Liu IL, Kumar VA(2007):** Prevalence of nondiabetic renal disease in diabetic patients. *Am J Nephrol.*,27(3):322–328.
 23. **Kasinath BS, Mujais SK, Spargo BH, Katz AI (1983):**Nondiabetic renal disease in patients with diabetes mellitus. *Am J Med.*,75(4):613–617.
 24. **Fioretto P, Mauer M(2010):** Diabetic nephropathy: diabetic nephropathy-challenges in pathologic classification. *Nat Rev Nephrol.*,6(9):508–510.
 25. **Tervaert TW, Mooyaart AL, Amann K, Cohen AH, Cook HT, Drachenberg CB, Ferrario F, Fogo AB, Haas M, de Heer E, Joh K, Noël LH, Radhakrishnan J, Seshan SV, Bajema IM, Bruijn JA (2010):**Renal Pathology Society. Pathologic classification of diabetic nephropathy. *J Am Soc Nephrol.*,21(4):556–563.