ScientificScholar®
Knowledge is power
Publisher of Scientific Journals

https://ijmsweb.com

Indian Journal of Medical Sciences

Article in Press

Original Article

Clinical correlates and pathology of non-diabetic renal disease in diabetes mellitus

Josephin Antoniammal[1], Jyothi Idiculla[2], Sara Chandy[1]

Departments of [1]General Medicine and [2]Internal Medicine, St. Johns Medical College and Hospital, Bengaluru, Karnataka, India.

ABSTRACT

Objectives: Early identification and differentiation of patients with non-diabetic renal disease (NDRD) from diabetic nephropathy (DN) or those with NDRD superimposed on DN improves the prognosis and reduces associated morbidity. The objectives of the study were to compare the clinical profile, nature of renal involvement, and etiopathogenesis (renal biopsy) of patients with isolated NDRD and NDRD superimposed on DN.

Materials and Methods: It is a descriptive study in patients with T2D and renal involvement suggestive of non-diabetic etiology further evaluated with renal biopsy and grouped as NDRD alone or NDRD with DN.

Results: Of the total 50, 66% were male, the mean age was 55.57 ± 12.28 years, and all were proteinuric. Overall, isolated NDRD and NDRD superimposed on DN were observed in 64% and 36% of patients, respectively. Diabetic retinopathy was absent in 82% of cases. The most common finding in isolated NDRD was membranous nephropathy, followed by immunoglobulin A (IgA) nephropathy and rapid progression of glomerular nephritis (RPGN). At the same time, in the NDRD and DN group, maximum patients displayed IgA nephropathy followed by acute tubular necrosis and RPGN. The incidence of atypical features of renal disease was almost twice as high in the isolated NDRD group than in the group with both NDRD + DN.

Conclusion: NDRDs are highly prevalent, and DN may superimpose these. Recognizing NDRD solely on the basis of clinical indicators is challenging. Therefore, histopathological analysis seems essential to accurately diagnose NDRD in diabetic patients to reduce the probability of missed NDRD diagnosis and initiate prompt treatment.

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

INTRODUCTION

Diabetic nephropathy (DN), also known as diabetic kidney disease, is a devastating complication of diabetes mellitus (DM) and is a leading cause of end-stage renal disease worldwide. Its prevalence across studies conducted globally lies between 11% and 38%. A cross-sectional study in India reported an incidence of more than 34%.[1,2] Non-diabetic renal disease (NDRD) is also reported in patients with type 2 DM within a broad range of 8–85% of biopsied cases.[3] A recently published observational study reported NDRD in more than 50% of patients with diabetes.[3] Thus, the prevalence of NDRD in patients with diabetes is high. Unlike DN, which is usually diagnosed based on the clinical and biochemical profile of the patients, NDRD requires a biopsy. It is critical to identify and differentiate patients with NDRD from DN or those with NDRD superimposed on DN because the management of both these conditions varies considerably. In addition, early diagnosis of NDRD improves the prognosis and reduces associated morbidity.

Therefore, the present study was planned to analyze the spectrum of NDRD in clinically indicated patients with atypical renal involvement and DM.

MATERIALS AND METHODS

The primary objective of the study was to assess patients with T2D with atypical renal involvement suggestive of non-diabetic etiology for NDRD. The clinical profile and nature of renal involvement of patients with isolated NDRD and those with NDRD superimposed on DN were compared. The secondary objective was to determine and compare the etiopathogenesis of nephropathy in these patients by renal biopsy.

It is a descriptive study which enrolled 50 patients with T2D and renal involvement suggestive of non-diabetic etiology

***Corresponding author:** Josephin Antoniammal, Department of General Medicine, St. Johns Medical College and Hospital, Bengaluru, Karnataka, India. sr.josejhc@gmail.com

Received: 19 December 2023 **Accepted:** 20 August 2024 **Epub ahead of print:** 08 October 2024 **Published:** XXXXX **DOI:** 10.25259/IJMS_115_2024

per inclusion criteria for further evaluation with renal biopsy. Adult patients with T2D for <5 years who demonstrated either nephrotic range proteinuria with normal renal function, declining renal function in the absence of diabetic retinopathy (DR), sudden unexplained deterioration of renal function, active urinary sediment, gross microscopic hematuria, or proven NDRD were included in the study. Patients with signs of infections, such as renal abscesses, acute and chronic pyelonephritis, those with renal calculi causing hydronephrosis, and those with signs of DN alone were excluded from the study.

After renal biopsy reports were available, they were classified into either NDRD alone or DN with co-existing NDRD. For each of the eligible patients, a detailed medical history was obtained, and a physical examination was performed. Data for patients and their features were documented on a standard pro forma, including demographics and the underlying primary renal disease. The patient features consist of demographic parameters (age and gender), body mass index (BMI) (kg/m^2), years of diabetes, the occurrence of DR, hypertension (%), hypothyroidism, ischemic heart disease (IHD %), glycated hemoglobin (HbA1c %), 24-h urinary protein (mg/day), hematuria, creatinine (mg/dL), estimated glomerular filtration rate (GFR) (mL/min), and urine protein creatine ratio. Patient characteristics were compared between the groups for analysis.

The etiological diagnosis was confirmed by histopathology. Glomerulonephritis was diagnosed in patients with a history of edema hypertension and documented a nephritic or nephrotic range of proteinuria. DN was also considered etiology in the presence of DR with albuminuria with a classical history of slow progression. NDRD was suspected in patients with sudden deterioration of renal function, hematuria, and worsening creatinine in the absence of DR. However, confirmation of DN and NDRD was obtained with a renal biopsy.

Written informed consent was obtained from each patient before the initiation of the study regarding the use of their clinical data for the publication, excluding any identifiable details. The research/study was approved by the Institutional Review Board at St John's Medical College Hospital, number IEC/1/931/2018/277, dated October 15, 2018.

Statistical analysis

All statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS) for Windows, version 20.0 (SPSS). Baseline clinical data are expressed as numbers, percentages, mean ± standard deviation, and median (interquartile range). Independent *t*-tests and Chi-square tests were used to compare baseline characteristics laboratory and histopathological findings, as appropriate. $P \leq 0.05$ would be considered statistically significant.

RESULTS

During the study period from September 2018 to January 2020, 50 patients were found to be eligible and included in the study analysis. The mean age of the patients was 55.57 ± 12.28 years, with 66% males. Among the 50 patients, histopathological analysis revealed that all patients had NDRD, with 36% superimposed on DN, while 64% had NDRD alone.

The demographics, clinical characteristics, and laboratory findings between these two groups are depicted in Table 1.

There was no significant difference in the mean age, gender, and BMI between the two groups. However, the duration of diabetes and incidence of DR were significantly greater in patients with both NDRD and DN than in those with NDRD alone. The proportion of patients with hypertension, IHD, and hypothyroidism was not significantly different between the two groups.

There was no significant difference between the two groups in the laboratory parameters investigating renal function and HbA1C [Table 1].

On comparison of the histopathological features [Table 2], it was observed that immunoglobulin A (IgA) nephropathy was the most common microscopic finding, followed by membranous nephropathy, acute tubular necrosis (ATN), and rapid progression of glomerular nephritis (RPGN), with no significant differences between the two groups. However, global glomerulosclerosis, membranoproliferative glomerulonephritis, Henoch-Schonlein purpura nephritis, light chain disease, and lupus nephritis were seen exclusively in patients in the NDRD group, while FSGS, thrombotic microangiopathy, hypertensive nephrosclerosis, and C3 glomerulonephropathy were exclusively seen in NDRD + DN group.

The patient profiles in both groups are shown in Table 3. The incidence of atypical features, namely, gross, microscopic hematuria, acute urinary sediment, sudden unexplained deterioration of renal function (elevated creatinine, decreased GFR, and proteinuria), declining renal function in the absence of DR, and nephrotic range of proteinuria was significantly greater in the isolated NDRD group than the group with NDRD + DN.

DISCUSSION

In our study of patients with diabetes, histopathological analysis revealed 36% with NDRD superimposed on DN and 64% with NDRD alone. Since the clinical profile prompts the conduct of a biopsy, the existing literature demonstrates a wide variation in the proportion of patients with an overlap of NDRD and DN between 8% and 85%; others found 12–79%, depending on criteria for biopsy. The widely

Table 1: Clinical features and laboratory findings of patients according to the pathologic classifications.

Patients characteristics	NDRD+DN (*n*=18)	NDRD (*n*=32)	*P*-value
Age (years) mean±SD	55.72±12.28	52.62±11.25	0.37
Sex (male, %)	12 (66.66)	21 (65.62)	0.59
BMI (kg/m^2) mean±SD	28.09±2.74	27.22±3.19	0.33
DM duration (years)	3.66±1.41	2.71±1.22	0.01*
Diabetic retinopathy (%)			
Yes	8 (16)	1 (2)	0.001*
No	10 (20)	31 (62)	0.001*
Hypothyroidism (%)			
Yes	3 (6)	4 (8)	0.69
No	15 (30)	28 (56)	0.69
IHD (%)			
Yes	3 (6)	3 (6)	0.65
No	15 (30)	29 (58)	0.65
Hypertension (%)			
Yes	17 (34)	23 (46)	0.06
No	1 (2)	9 (18)	0.06
Laboratory investigations			
HbA1C mean±SD	6.99±1.29	6.67±0.91	0.31
Renal function parameters			
Proteinuria (mg/day)	477.38±507.97	402.29±413.82	0.58
Hematuria (%)			
Yes	7 (14)	13 (26)	0.57
No	11 (21)	19 (38)	0.57
Baseline creatinine (mg/dL)	2.23±1.7	2.1±1.9	0.89
First serum creatinine (mg/dL)	3.56±3	3.76±4.27	0.86
Current serum creatinine (mg/dL)	3.12±2.33	3.05±2.83	0.93
eGFR (MDRD) (mL/min)	44.37±37.64	51.94±43.7	0.54
PCR	10.18±6.72	7.4±6.68	0.17

BMI: Body mass index, DM: Diabetes mellitus, DN: Diabetic nephropathy, IHD: Ischemic heart disease, eGFR: Estimated glomerular filtration rate, HbA1c: Glycated hemoglobin, MDRD: Modification of diet in renal disease, PCR: Urine protein creatine ratio, NDRD: Non-diabetic renal disease, SD: Standard deviation, *The difference between NDRD and DN compared to those with NDRD alone is statistically significant.

varying data further underscore the need for more evidence generation in diabetic patients manifesting renal disease. Two observational studies have previously reported an incidence of isolated NDRD in 18–20% and NDRD and DN in 29–33% of biopsied patients.[3,4] The results of our study are similar to that reported in India and other regions where incidence was more than 50% by Wilfred *et al.* (68.81%) and Yang *et al.* (61%) Prakash in their respective studies.[5-7] The wide variation in previously reported results would also be explained by the inclusion criteria of the duration of diabetes. We applied a cutoff of <5 years and, therefore, possibly had more patients with NDRD than DN. The mean duration overall of diabetes in our study was between 3.1 years, while in other studies, it was 3–8 years and 4–6 years.[3,4] The duration of diabetes was clearly longer in those with NDRD superimposed on DN compared to isolated NDRD. This observation is in agreement with the previously reported studies, which also found a significant difference in the duration of diabetes between these groups.[3-8] The lesser duration of diabetes in patients with renal manifestations per se is suggestive of NDRD than DN.[4]

The incidence of DR was also significantly higher in those with DN than without. In the isolated NDRD group, merely one patient had DR. Absence of retinopathy has been stated to be one of the predictors of NDRD, but presence does not exclude NDRD, as noted in our study.[8] The presence of retinopathy in those with DN also corroborates the association between the duration of diabetes and microvascular complications.

Surprisingly, there was no difference between the incidence of hypertension, glycemic control mean levels of proteinuria, or mean renal function parameters between the two groups. Other studies have reported similar findings, while still others have found direct associations.[4,8,9] This further highlights the need for histopathological analysis and discourages complete reliance on clinical parameters for prompting suspicion of NDRD, which could be inconsistent.

Table 2: Comparison of histopathological diagnosis among study subjects (*n*=50).

Histopathological findings	DN+NDRD (*n*=18) (%)	NDRD (*n*=32) (%)	*P*-value
IgA	6 (33.34)	6 (18.75)	0.25
Membranous nephropathy	1 (5.55)	9 (28.12)	0.058
ATN	4 (22.23)	3 (9.37)	0.21
RPGN	2 (11.12)	4 (12.5)	0.88
Global glomerulosclerosis	0	3 (9.375)	0.18
MPGN	0	3 (9.375)	0.18
FSGS	1 (5.55)	1 (3.125)	0.67
Thrombotic microangiopathy	2 (11.12)	0	0.056
HN	1 (5.55)	0	0.18
HSP nephritis	0	1 (3.125)	0.45
Light chain disease	0	1 (3.125)	0.45
Lupus nephritis	0	1 (3.125)	0.45
C3 glomerulonephropathy	1 (5.55)	0	0.18

ATN: Acute tubular necrosis, DN: Diabetic nephropathy, FSGS: Focal segmental glomerulosclerosis, HN: Hypertension, HSP nephritis: Henoch-Schonlein purpura nephritis, IgAN: Immunoglobulin A nephropathy, RPGN: Rapidly progression of glomerular nephritis, MPGN: Mesangioproliferative glomerular nephritis, NDRD: Non-diabetic renal disease

Table 3: Patient profile in NDRD+DN versus NDRD alone group.

	NDRD+DN (*n*=18) (%)	NDRD (*n*=32) (%)	*P*-value
Gross microscopic hematuria	6 (33.34)	21 (65.26)	0.03
Acute urinary sediment	6 (33.34)	21 (65.26)	0.03
Sudden unexplained deterioration of renal function (elevated creatinine, decreased GFR, proteinuria)	10 (55.55)	28 (87.5)	0.012
Declining renal function in the absence of DR	7 (38.89)	26 (81.25)	0.002
Nephrotic range of proteinuria	15 (83.34)	32 (100)	0.01

DN: Diabetic nephropathy, DR: Diabetic retinopathy, GFR: Glomerular filtration rate, NDRD: Non-diabetic renal disease

The most common finding in isolated NDRD was membranous nephropathy, followed by IgA nephropathy and RPGN, while in the NDRD and DN group, maximum patients displayed IgA nephropathy, followed by ATN and RPGN. These are common nephropathies reported previously in diabetic patients with NDRD.[4,10-13] Overall, IgA was the most frequent NDRD, as also demonstrated by a meta-analysis of 48 studies.[14]

Among the two patient groups, there were significant differences in the patient profiles. The atypical characteristics were significantly greater in patients with isolated NDRD than in the NDRD+DN group. The incidence of atypical features was almost twice in the isolated NDRD group than in the group with NDRD+DN. Thus, NDRDs are highly prevalent and may superimpose DN. Therefore, histopathological analysis seems essential to diagnose NDRD in diabetic patients to reduce the probability of missed NDRD diagnosis.

Our study has certain limitations. We selected patients based on a higher likelihood of NDRD with a short duration of diabetes. A DN-only group would have provided more clear comparisons between NDRD and non-NDRD.

CONCLUSION

Our data show that a considerable proportion of patients have DN-superimposed NDRD. Atypical features of renal impairment with lower incidence or absence of retinopathy with nephrotic range proteinuria and shorter duration of diabetes are clinical indicators of NDRD. However, though there was a significant difference in atypical renal manifestation among patients with isolated NDRD and combined NDRD with DN, recognizing NDRD solely on the basis of clinical indicators is challenging. Therefore, histopathological analysis is key.

Ethical approval

The research/study was approved by the Institutional Review Board at St John's Medical College Hospital, number IEC/1/931/2018/277, dated October 15, 2018.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript, and no images were manipulated using AI.

REFERENCES

1. Al-Shamsi S, Regmi D, Govender RD. Chronic kidney disease in patients at high risk of cardiovascular disease in the United Arab Emirates: A population-based study. PLoS One 2018;13:e0199920.
2. Kung K, Chow KM, Hui EM, Leung M, Leung SY, Szeto CC, *et al.* Prevalence of complications among Chinese diabetic patients in urban primary care clinics: A cross-sectional study. BMC Fam Pract 2014;15:8.
3. Eswarappa M, Suryadevara S, Rajashekar R, Mahesh Kumar KB, Gurudev KC, Tyagi P, *et al.* Non-diabetic kidney disease in diabetic population: A single-center study from South India. Cureus 2022;14:e23899.
4. Kritmetapak K, Anutrakulchai S, Pongchaiyakul C, Puapairoj A. Clinical and pathological characteristics of non-diabetic renal disease in type 2 diabetes patients. Clin Kidney J 2018;11:342-7.
5. Wilfred DC, Mysorekar VV, Venkataramana RS, Eshwarappa M, Subramanyan R. Non-diabetic renal disease in type 2 diabetes mellitus patients: A clinicopathological study. J Lab Physicians 2013;5:94-9.
6. Yang Z, Feng L, Huang Y, Xia N. A differential diagnosis model for diabetic nephropathy and non-diabetic renal disease in patients with type 2 diabetes complicated with chronic kidney disease. Diabetes Metab Syndr Obes 2019;12:1963-72.
7. Prakash J. Non-diabetic renal disease (NDRD) in patients with type 2 diabetes mellitus (type 2 DM). J Assoc Physicians India 2013;61:194-9.
8. Yenigun EC, Dede F, Ozturk R, Turgut D, Koc E, Piskinpasa SV, *et al*. Non-diabetic renal disease in diabetes mellitus: Clinical features and renal biopsy findings. Hippokratia 2015;19:148-52.
9. Mak SK, Gwi E, Chan KW, Wong PN, Lo KY, Lee KF, *et al.* Clinical predictors of non-diabetic renal disease in patients with non-insulin-dependent diabetes mellitus. Nephrol Dial Transplant 1997;12:2588-91.
10. Tone A, Shikata K, Matsuda M, Usui H, Okada S, Ogawa D, *et al.* Clinical features of non-diabetic renal diseases in patients with type 2 diabetes. Diabetes Res Clin Pract 2005;69:237-42.
11. Zhuo L, Ren W, Li W, Zou G, Lu J. Evaluation of renal biopsies in type 2 diabetic patients with kidney disease: A clinicopathological study of 216 cases. Int Urol Nephrol 2013;45:173-9.
12. Mou S, Wang Q, Liu J, Che X, Zhang M, Cao L, *et al*. Prevalence of non-diabetic renal disease in patients with type 2 diabetes. Diabetes Res Clin Pract 2010;87:354-9.
13. Koyama A, Kobayashi M, Yamaguchi N, Yamagata K, Takano K, Nakajima M, *et al.* Glomerulonephritis associated with MRSA infection: A possible role of bacterial superantigen. Kidney Int 1995;47:207-16.
14. Fiorentino M, Bolignano D, Tesar V, Pisano A, Biesen WV, Tripepi G, *et al.* Renal biopsy in patients with Diabetes: A pooled meta-analysis of 48 studies. Nephrol Dial Transplant 2017;32:97-110.

How to cite this article: Antoniammal J, Idiculla J, Chandy S. Clinical correlates and pathology of non-diabetic renal disease in diabetes mellitus. Indian J Med Sci. doi: 10.25259/IJMS_115_2024