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Renal outcomes and clinical course of nondiabetic renal diseases in patients with type 2 diabetes

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Background/Aims: In several recent studies, renal biopsies in patients with type 2 diabetes and renal disease have revealed a heterogeneous group of disease entities. Our aim was to study the prognosis and clinical course of nondiabetic renal disease (NDRD) and to determine risk factors for NDRD in patients with type 2 diabetes.

Methods: Renal biopsy reports of 110 patients with type 2 diabetes who were seen at Kyung Hee University Medical Center and Kyung Hee University Hospital at Gangdong, Seoul, Korea between January 2000 and December 2011 were retrospectively analyzed.

Results: Of 110 patients with type 2 diabetes, 41 (37.3%) had diabetic nephropathy (DN), 59 (53.6%) had NDRD, and 10 (9.1%) had NDRD superimposed on DN. Immunoglobulin A nephropathy (43.5%) was the most common NDRD. Patients with NDRD had a shorter duration of diabetes, lower frequency of diabetic retinopathy, and better renal outcomes, which might have resulted from the use of aggressive disease-specific treatments such as steroids and immunosuppressants in patients with NDRD.

Conclusions: Compared with DN, NDRD was associated with better renal outcomes in patients with type 2 diabetes, as evidenced by a higher cumulative renal survival rate and lower rate of end-stage renal disease (ESRD). Shorter duration of diabetes and absence of retinopathy were independent predictors of NDRD in patients with type 2 diabetes and renal involvement. Renal biopsy is recommended for patients with type 2 diabetes and risk factors for NDRD, to obtain an accurate diagnosis, prompt initiation of disease-specific treatment, and ultimately better renal outcomes with the avoidance of ESRD.

Keywords: Non-diabetic renal disease; Diabetic nephropathies; Diabetes mellitus, type 2

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INTRODUCTION

Diabetes mellitus (DM) has become the most common single cause of end-stage renal disease (ESRD) worldwide [1-3]. Up to 50% of patients with type 2 DM manifest with renal involvement, as evidenced by albuminuria [3-5]. However, renal diseases other than diabetic nephropathy (DN) can occur in patients with DM.

Renal biopsy remains as integral part of clinical nephrology practice because the information it provides is pivotal for making a specific diagnosis, for planning patient management, and for evaluating disease activ-

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ity and prognosis [6]. However, due to its invasiveness, renal biopsy is not routinely performed in patients with DM presenting with proteinuria. This is potentially problematic, as renal biopsies from patients with DM and renal disease have revealed a heterogeneous group of renal lesions. In previous reports, the rate of nondiabetic renal disease (NDRD) ranged from 27% to 79% based on renal biopsies performed in patients with DM and renal involvement [7-15]. Some of these disease entities are remittable, and some cases are treatable when correctly intercepted. Thus, the importance of an accurate diagnosis to a successful renal outcome cannot be underestimated.

Unfortunately, distinguishing between NDRD and DN in patients with DM remains challenging, and there are no clear indications for renal biopsy. Furthermore, the nature of NDRD in patients with DM has not yet been documented in Korea. This study was carried out to investigate the clinical course and prognosis of NDRD in a Korean population, to identify predictors of NDRD in patients with DM and renal involvement, and to establish possible indications for renal biopsies in patients with DM.

METHODS

We retrospectively reviewed renal biopsy specimens of 110 adult patients with type 2 DM, as defined by the World Health Organization, between January 2000 and December 2011 at two nephrology centers, Kyung Hee University Medical Center and Kyung Hee University Hospital at Gangdong, Seoul, Korea. Patients with malignancy, inadequate biopsy, incomplete medical records, or a history of kidney transplantation were excluded. The indications for biopsy were retrospectively assessed according to the following categories: 1) unexplained acute kidney injury, 2) sudden onset of heavy proteinuria, 3) hematuria, 4) sudden increase in serum creatinine level in the absence of retinopathy, and 5) other.

Written consent was obtained from all patients. All biopsy specimens were prepared by standard methods and examined by the same group of pathologists and technicians. Light microscopy, immunofluorescence, and electron microscopy were performed in all cases. Pathology reports were reviewed and patients were classified into three groups: group I, isolated DN; group II, NDRD superimposed on DN; and group III, isolated NDRD. The following data were collected at the time of renal biopsy: age, sex, height, weight, duration of diabetes, presence of retinopathy, urinalysis with microscopy, underlying medical conditions, and events leading to the renal biopsy. Additional parameters such as long axis length of the kidney and levels of blood urea nitrogen, serum cholesterol, serum albumin, serum creatinine, and glycosylated hemoglobin (HbA1c) were also collected. Hematuria was defined as five or more red blood cells per high power field noted on the most recent urinalysis prior to biopsy. Proteinuria was quantified using the spot urine protein to creatinine ratio or 24-hour urine total protein. Diabetic retinopathy was diagnosed in the presence of background retinopathy with or without proliferative changes on fundoscopy and fluorescein angiography.

Statistical analysis

The results are presented as means ± SD. Differences between groups were assessed with the *t* test or analysis of variance for continuous variables, and with the chi-square test for categorical variables. Kaplan-Meier analysis was used to compare unadjusted ESRD-free survival. Independent predictors of NDRD were determined by multiple logistic regression analysis. Values of $p < 0.05$ were considered to indicate significance. Statistical analyses were performed using PASW Statistics version 18 (IBM Co., Armonk, NY, USA).

RESULTS

Clinical predictors of NDRD

A total of 110 Korean patients with type 2 DM were included in this study. Of these, 41 patients (37.3%) had a pathologic diagnosis of DN, 10 (9.1%) had NDRD combined with DN, and 59 (53.6%) had NDRD without evidence of DN. Table 1 shows the types of NDRDs detected. The most common nephropathy among the 59 patients with NDRD was immunoglobulin A nephropathy (IgAN), which accounted for 43.5% of all NDRD. Membranous glomerulonephritis (MGN) accounted for 14.5%, followed by crescentic glomerulonephritis

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(7.2%) and tubulointerstitial nephritis (4.3%). Indications for biopsy included sudden onset of heavy proteinuria (> 3.5 g/day) in 47 cases, hematuria in 33, unexplained acute kidney injury in 22, sudden increase in serum creatinine level in the absence of retinopathy in three, and other reasons in five cases (Table 2).

Table 3 summarizes the baseline patient demographics along with clinical and biochemical parameters. No differences in age, gender distribution, or body mass index were observed among the three groups. However, patients with isolated DN had a significantly longer history of diabetes before biopsy than those with NDRD (12.85 ± 7.54 years vs. 3.4 ± 2.64 years vs. 4.13 ± 4.79 years, I vs. II vs. III; $p < 0.001$). Notably, hematuria occurred more often in the presence of NDRD (34.1% vs. 60% vs. 59.3%, I vs. II vs. III; $p = 0.04$). The differences in baseline serum creatinine levels and urinary protein excretion did not reach significance. Albumin, total cholesterol, serum IgA level, and serum IgG level did not differ significantly between groups. HbA1c levels were higher in patients with isolated DN than in patients with NDRD superimposed on DN (8.43% ± 2.49% vs. 6.18% ± 0.68%, respectively; $p = 0.02$). No difference in kidney size or the incidence of hypertension was observed between the groups. A higher prevalence of diabetic retinopathy was evident in patients with isolated DN than in those with NDRD (75.6% vs. 10% vs. 20.3%, I vs. II vs. III; $p < 0.001$). Multiple logistic regression analysis revealed that diabetes duration and retinopathy were independent factors correlated with NDRD (Table 4). These findings are in agreement with previous studies that also identified

Table 1. Pathological findings in group II (nondiabetic renal disease superimposed on diabetic neuropathy) and group III (nondiabetic renal disease alone)

Type of NDRD	Group II (n = 10)	Group III (n = 59)	Total (NDRD ± DN) (n = 69)
IgA nephropathy	6	24	30 (43.5)
Membranous glomerulonephritis	0	10	10 (14.5)
Crescentic glomerulonephritis	1	4	5 (7.2)
Membranoproliferative glomerulonephritis	0	1	1 (1.4)
Henoch-Schönlein purpura	0	2	2 (2.9)
Minimal change disease	1	1	2 (2.9)
Lupus nephritis	0	1	1 (1.4)
Focal segmental glomerulosclerosis	0	1	1 (1.4)
Tubulointerstitial nephritis	0	3	3 (4.3)
Other	2	12	14 (20.3)

Values are presented as number (%). Group II, nondiabetic renal disease (NDRD) superimposed on DN; group III, isolated NDRD.
DN, diabetic nephropathy; IgA, immunoglobulin A.

Table 2. Indications for renal biopsy in patients with diabetes

Reason for biopsy	Group I (n = 41)	Group II (n = 10)	Group III (n = 59)
Sudden heavy proteinuria (n = 47)	25 (60.9)	2 (20)	20 (33.8)
Hematuria (n = 33)	7 (17.0)	4 (40)	22 (37.2)
Acute kidney injury (n = 22)	9 (21.9)	4 (40)	9 (15.2)
Sudden increase in serum Cr (n = 3)	0 (0)	0 (0)	3 (5.0)
Others (n = 5)	0 (0)	0 (0)	5 (8.4)

Values are presented as number (%). Group I, isolated diabetic nephropathy (DN); group II, nondiabetic renal disease (NDRD) superimposed on DN; group III, isolated NDRD.

Table 3. Patient demographics and clinical and biochemical parameters

Parameter	Group I (n = 41)	Group II (n = 10)	Group III (n = 59)	*p* value[a]
Sex, male:female	26:15	5:5	37:22	NS
Age, yr	52.60 ± 10.34	43.0 ± 9.30	54.34 ± 12.47	NS
Diabetes duration, yr	12.85 ± 7.54	3.4 ± 2.64[b]	4.13 ± 4.79[c]	< 0.001
Body mass index, kg/m^2	24.32 ± 2.82	25.08 ± 3.58	25.39 ± 3.36	NS
Retinopathy	31 (75.6)	1 (10)[b]	12 (20.3)[c]	< 0.001
Proteinuria, mg/day	6,614.97 ± 4,236.41	2,458.80 ± 2,468.94	4,809.72 ± 4,977.02	NS
Hematuria	14 (34.1)	6 (60)[b]	35 (59.3)[c]	0.04
Serum creatinine, mg/dL	2.15 ± 1.42	2.02 ± 1.05	2.69 ± 4.41	NS
Kidney long axis, cm	10.61 ± 1.42	11.06 ± 0.63	11.18 ± 1.48	NS
Serum total cholesterol, mg/dL	242.17 ± 72.03	215.80 ± 92.31	210.68 ± 77.59	NS
Serum albumin, g/dL	2.84 ± 0.77	3.18 ± 1.36	3.09 ± 0.89	NS
Serum IgG, mg/dL	822.30 ± 71.61	1,060.00 ± 131.55	1,004.81 ± 58.11	NS
Serum IgA, mg/dL	274.74 ± 25.68	282.50 ± 47.17	313.57 ± 20.59	NS
HbA1c, %	8.43 ± 2.49	6.18 ± 0.68[b]	7.26 ± 1.92	0.02
Hypertension	29 (70.7)	5 (50)	45 (76.3)	NS

Values are presented as mean ± SD or number (%). Group I, isolated diabetic nephropathy (DN); group II, nondiabetic renal disease (NDRD) superimposed on DN; group III, isolated NDRD.
IgG, immunoglobulin G; IgA, immunoglobulin A; HbA1c, glycosylated hemoglobin.
[a]*p* value from chi-square test and analysis of variance.
[b]Significant difference between group I and group II.
[c]Significant difference between group I and group III.

Table 4. Clinical predictors of nondiabetic renal disease by multiple logistic regression analysis

Variable	β-Estimate	95% CI	Odds ratio	*p* value
Age	0.054	0.972–1.148	1.056	0.199
Diabetes duration	-0.151	0.739–0.999	0.860	0.049
Retinopathy	-3.648	0.003–0.265	0.026	0.002
Hematuria	0.815	0.485–10.512	2.259	0.299
Proteinuria	0.000	1.000–1.000	1.000	0.737
Serum creatinine	0.433	0.945–1.148	1.543	0.083
HbA1c	0.119	0.899–1.409	1.126	0.301

CI, confidence interval; HbA1c, glycosylated hemoglobin.

the absence of retinopathy and short diabetes duration as strong predictors of NDRD [7-11,15].

Complications after renal biopsy

Renal color Doppler ultrasonography was performed after renal biopsy in all subjects to check for complications related to the procedure. Complications after renal biopsy occurred in 25.4% (28/110) of the patients, with the majority of the patients (74.6%, n = 82) experiencing no complications after renal biopsy. The prevalence of complications did not differ significantly among the three groups. The most common complication was perirenal bleeding (19%, n = 21), followed by arteriovenous fistula (6.4%, n = 7). All complications resolved spontaneously within 48 hours. No life-threatening complications requiring massive transfusion, arterial embolization, or surgery occurred.

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Clinical course and prognosis

Table 5 shows the medications used to treat underlying diseases. No difference was observed in the use of angiotensin converting enzyme inhibitors or angiotensin receptor blockers among the three groups. However, the use of steroids and immunosuppressants such as cyclosporine was predominant in patients with NDRD (steroids, 2.4% vs. 60% vs. 61%, I vs. II vs. III, $p < 0.001$; immunosuppressants, 7.3% vs. 50% vs. 28.8%, I vs. II vs. III, $p = 0.004$). Patients with isolated DN tended to show more rapid deterioration of renal function, although the difference failed to reach significance (Table 5). Patients with DN were associated with a higher final serum creatinine level and higher urinary protein excretion. Patients with NDRD has a higher cumulative renal survival rate (percentage of patients not reaching ESRD) compared with patients with isolated DN (Fig. 1), who were more likely to progress to ESRD and require dialysis (23.5% vs. 0% vs. 5.5%, I vs. II vs. III; $p < 0.001$ for I vs. III, $p = 0.006$ for I vs. II) (Table 5).

DISCUSSION

In this study, patients with type 2 DM who underwent renal biopsy were divided into three groups according to the underlying pathology of the renal disease: DN alone, NDRD combined with DN, or NDRD alone. More than half of the patients (62.7%) had NDRD. This finding is in accordance with recent studies reporting NDRD prevalence rates of 27% to 79% in patients with DM who underwent renal biopsy for various reasons. IgAN was the most common disease entity in the present study, accounting for 43.5% of all NDRD cases. This may explain the positive correlation between NDRD and hematuria. According to previous reports

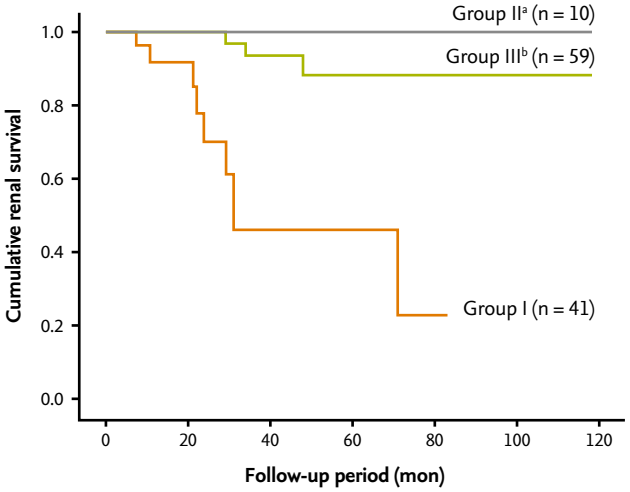

Figure 1. Renal survival in the three groups. Percentage of patients not developing end-stage renal disease by the last follow-up. Group I, isolated diabetic nephropathy (DN); group II, nondiabetic renal disease (NDRD) superimposed on DN; group III, isolated NDRD. [a]$p = 0.006$ for I vs. II, [b]$p < 0.001$ for I vs. III.

Table 5. Treatment modality and renal outcomes

Treatment/outcome	Group I (n = 41)	Group II (n = 10)	Group III (n = 59)	*p* value[a]
Final serum creatinine, mg/dL	3.65 ± 2.94	1.91 ± 1.75[b]	1.81 ± 2.06[c]	0.004
Final proteinuria, mg/day	6,017.50 ± 4,938.85	1,174.0 ± 2,321.00[b]	1,554.82 ± 2,634.73[c]	< 0.001
Development of ESRD[d]	8 (19.5)	0(0)[b]	3 (5.0)[c]	< 0.001
Rate of change in CrCl, mL/min/1.73 m²/mon	-1.15 ± 1.53	0.46 ± 0.38	0.77 ± 5.21	NS
Use of ACEi/ARB	33 (80.5)	6 (60)	42 (71.2)	NS
Use of steroid	1 (2.4)	6 (60)[b]	36 (61.0)[c]	< 0.001
Use of immunosuppressants	3 (7.3)	5 (50)[b]	17 (28.8)[c]	0.004

Values are presented as mean ± SD or number (%). Group I, isolated diabetic neuropathy (DN); group II, nondiabetic renal disease (NDRD) superimposed on DN; group III, isolated NDRD.
ESRD, end-stage renal disease; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.
[a]*p* value from chi-square test, ANOVA, and log-rank survival analysis.
[b]Significant difference between group I and group II.
[c]Significant difference between group I and group III.
[d]ESRD, defined as CrCl ≤ 15 mL/min/1.73 m² (chronic kidney disease stage 5).

Table 6. Review of the literature on nondiabetic renal disease in type 2 diabetes mellitus

Country	Reference	Total no. of patients	Percentage of NDRD, includes concurrent NDRD and DN (n)	Most common pathologic diagnosis	Clinical predictors of NDRD[a]
South Korea	Lee et al. [9]	22	63.6 (14)	IgAN	1, 2, 3, 5
Hong Kong	Wong et al. [15]	68	65 (44)	IgAN	1, 2, 3, 4, 5
	Mak et al. [14]	51	33.3 (17)	IgAN	
Taiwan	Lin et al. [8]	50	52 (26)	AIN	4, 6
China	Zhou et al. [11]	110	45.5 (50)	IgAN	1, 2, 3, 5, 6
Saudi Arabia	Ghani et al. [12]	31	45.2 (14)	Crescentic GN	1, 4
India	Soni et al. [7]	160	72.5 (116)	AIN	1, 2, 4
USA	Pham et al. [2]	233	72.5 (169)	FSGS	1, 4

NDRD, nondiabetic renal disease; DN, diabetic nephropathy; IgAN, immunoglobulin A nephropathy; AIN, acute interstitial nephritis; GN, glomerulonephritis; FSGS, focal segmental glomerulosclerosis.
[a]Clinical predictors of NDRD: 1) lack of retinopathy, 2) short duration of DM, 3) hematuria (microscopic red blood cell [RBC] or dysmorphic RBC on urinanalysis), 4) less prominent proteinuria, 5) lower glycosylated hemoglobin, and 6) other.

on NDRD in patients with type 2 DM (Table 6), patients in southeast Asia, namely, South Korea, Hong Kong, Taiwan, and China, had a high incidence of IgAN. Our finding was comparable to these previous results. Moreover, IgAN is the most common primary glomerulonephritis in the general South Korean population, with a prevalence of 28.3% to 50.6% depending on the study [16,17]. In contrast, a recent study from the United States reports focal segmental glomerulosclerosis as the most common glomerular disease in adults, suggesting a change in the pattern of glomerular diseases [18]. The differences in prevalence patterns for glomerulopathies among various populations of patients with type 2 DM may reflect hereditary and racial predispositions for specific glomerulopathies.

Diabetic retinopathy was seen more frequently among patients with DN in the present study, as in other recent studies (Table 6). This finding confirms the accepted view that the absence of retinopathy indicates the possibility of NDRD and thus warrants a renal biopsy. Because DN is a chronic complication of diabetes, occurring 5 to 10 years after onset or diagnosis of diabetes, patients with DN in the present study had significantly longer disease duration. Thus, shorter duration of type II DM was an indicator of NDRD in the present patient population. Furthermore, although the difference was not significant, patients with NDRD in our study tended to have higher serum IgG levels (Table 3). In contrast, Weng et al. [19] reported a reduced serum IgG level as an indicator of NDRD in patients with type 2 DM. It is possible that our results are inaccurate because serum IgG levels were not available for all study subjects. A more structured, large-scale study may resolve this apparent discrepancy.

Nephrologists are often reluctant to perform a renal biopsy because of the potential complications related to the procedure. However, our retrospective review found renal biopsy to be a relatively safe procedure, with minor complications reported in 25.4% of cases and no reports of serious complications requiring massive transfusion, intervention, or surgery.

It is important to note that IgAN and MGN combined accounted for more than 50% of all NDRDs in the present study. These disease entities are potentially modifiable with agents other than standard renin angiotensin blockers. This high incidence of potentially treatable diseases may explain the more prevalent use of steroids and immunosuppressants in the NDRD groups in our study. Furthermore, this aggressive medical intervention might have contributed to the better renal outcomes observed in the NDRD groups. Despite similar baseline serum creatinine levels at the time of renal biopsy, the DN group experienced a faster rate of decline in creatinine clearance and a greater likelihood of progression to ESRD compared with the NDRD groups (Table 5). Although treatment did not always result in complete remission, even partial remission prolonged renal survival in our

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study. Notably, the prognosis for patients with NDRD and DN (group II) was better than the prognosis for patients with DN alone (group I). One possible explanation for the better prognosis is that patients in group II had a relatively shorter duration of diabetes and thus less severe DN compared with the patients in group I. None of the biopsies in group II patients showed pathological findings of advanced DN, such as nodular glomerulosclerosis (Kimmelstiel-Wilson) or diabetic sclerosis. All glomerular lesions in group II belonged to class I (isolated glomerular basement membrane thickening) or class IIa (mild mesangial expansion), as defined by the Renal Pathology Society classification. The clinical manifestations in group II could be attributed primarily to NDRD, which is more readily reversible and responsive to steroids and immunosuppressants, with a better prognosis. Nevertheless, as there were only 10 patients with combined NDRD and DN (group II), our data for analyzing outcomes in this group are limited. A study with a larger number of patients may clarify these results.

The rapidly escalating incidence of DM is associated with increased morbidity and mortality worldwide, and the complications associated with the disease have attracted much attention. DN affects up to 50% of patients with DM [3,4]. The indications for renal biopsy in type 1 DM have been somewhat established: microhematuria, absence of diabetic retinopathy, uncharacteristic change in renal function, or immunological abnormalities [20]. Unfortunately, the indications are not as clear in patients with type 2 DM. Renal involvement in patients with type 2 DM is frequently overlooked, and when DN is diagnosed, it is almost always based solely on clinical findings. A renal biopsy is rarely performed to confirm the etiology because there is no formal justification or uniform pathological classification system for DN that is closely related to clinical renal outcomes or that may improve clinical management [7,21]. However, in several recent studies, renal biopsies from patients with type 2 DM and renal disease have revealed a heterogeneous group of disease entities [7-15]. Furthermore, because renal survival can be prolonged with early initiation of disease-specific therapy in patients with DM and NDRD, a swift and accurate diagnosis is crucial, necessitating established indications for renal biopsy in patients with type 2 DM and renal involvement. Through this retrospective study, we have identified shorter duration of diabetes and absence of retinopathy as factors associated with NDRD. For patients having these factors, a renal biopsy should be recommended to allow for precise diagnosis and prompt treatment, leading to better renal survival and the avoidance of ESRD.

Some limitations of our study should be discussed. Because most of our study patients were initially selected for renal biopsy owing to a high suspicion of underlying NDRD, our results may overestimate the true number of patients with NDRD. Although hematuria was the sole indicator for renal biopsy in 33 patients, the presence of red cell casts or acanthocytes was not evaluated, and the amount of hematuria was not quantified. Moreover, the results cannot be readily extrapolated to the general population of patients with DM and renal involvement. Additional limitations of the present study are its retrospective design, small sample size, and heterogeneous treatment modalities.

In conclusion, our study population represented a select group with high clinical suspicion of NDRD, and renal biopsies showed that more than half of the patients had NDRD. IgAN was the most common

KEY MESSAGE

1. The renal involvements in type 2 diabetes are frequently overlooked and designated as having diabetic nephropathy. However, renal biopsies from type 2 diabetic patients with renal disease comprise a heterogenous group of disease entities, some of which are remittable and in some cases, treatable.
2. In type 2 diabetic patients manifesting renal involvement, short duration of diabetes and absence of retinopathy are independent predictors of nondiabetic renal disease (NDRD).
3. From this study, we have recognized that patients with NDRD are associated with better renal outcomes. Therefore, renal biopsy should be recommended to type 2 diabetic patients with risk factors of NDRD for accurate diagnosis, prompt initiation of disease-specific treatment and ultimately, better renal outcomes.

NDRD, followed by MGN. In patients with type 2 DM manifesting renal involvement, a short duration of diabetes (4.13 ± 4.79 years in this study) and the absence of retinopathy were independent predictors of NDRD. Patients with NDRD were associated with better renal outcomes, as evidenced by a higher cumulative renal survival rate. Especially considering its relative safety and low rate of serious complications, renal biopsy is recommended for patients with type 2 DM and risk factors for NDRD, to obtain an accurate diagnosis, prompt initiation of disease-specific treatment, and ultimately better renal outcomes.

Conflict of interest

No potential conflict of interest relevant to this article is reported.

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