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Non-diabetic Renal Disease in Patients with Non-insulin Dependent Diabetes Mellitus

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Abstract

The diagnosis of diabetic nephropathy (DN) is almost always based on clinical grounds. The diagnosis is supported by a long history of diabetes, evidence of target organ damage and proteinuria preceding azotemia. The validity of this clinical approach is well established in insulin dependent diabetes mellitus but not in non-insulin dependent diabetes mellitus (NIDDM). It is thus important to determine which patients with NIDDM accompanied by non-diabetic renal disease (NDRD) should have a biopsy. However, factors clinically associated with NDRD in patients with NIDDM remain unclear. Therefore we reviewed clinical data, laboratory data and renal biopsies from 22 NIDDM patients who underwent renal biopsy between 1992 and 1998 in Wonju Christian Hospital. From this data, we identified important features that would discriminate between DN and NDRD. There were 8 women and 14 men. Age ranged from 33 to 68 (51.2 ± 10.7) years. The duration of diabetes at biopsy ranged from 0 to 13 (4.2 ± 4.2) years. Nephrotic syndrome was present in 13 patients. The patients with NDRD ($n=14$) and DN ($n=8$) had comparable 24-hour proteinuria, 24-hour albuminuria, creatinine clearance, serum creatinine, albumin, as well as incidences of neuropathy and hypertension. The significant factors that predict the NDRD included a short duration of the diabetes mellitus, the presence of dysmorphic red blood cells in urine, the absence of retinopathy and HbA1c below 9% ($p<0.05$, respectively). NDRD included IgA nephropathy ($n=6$), minimal change disease ($n=3$), membranous nephropathy ($n=3$), membranous lupus nephritis ($n=1$) and acute interstitial nephritis ($n=1$). Multiple logistic regression analysis revealed that the short duration of DM and the absence of retinopathy were factors significantly associated with NDRD. In summary, when there is a short duration of diabetes mellitus, or an absence of retinopathy seen in patients with NIDDM, then renal biopsy in diabetic patients aids in the detection of NDRD.

Key Words: Non-diabetic renal disease, non-insulin dependent diabetes mellitus, renal biopsy

INTRODUCTION

It has been well demonstrated that renal disease in patients suffering from insulin dependent diabetes mellitus (IDDM) for over 10 years is usually the result of diabetic nephropathy (DN), as proven histologically in >95% of these patients.[1-3] Therefore, renal biopsy in this setting is not diagnostically useful. The temporal profile of events that characterize DN in IDDM is considered so predictable, and the association between microangiopathy in the retina and in the kidney is so consistent,[4,5] that diabetic patients with proteinuria are presumed to have DN, usually without tissue diagnosis. However, in non-insulin dependent diabetes mellitus (NIDDM) patients, proteinuria may reflect a concurrent renal lesion superimposed on DN or an unrelated disorder. The detection of superimposed primary non-diabetic renal disease (NDRD) in diabetic patients has an obvious prognostic and therapeutic importance. However, clinically associated factors with NDRD in patients with NIDDM has not been fully determined.

Therefore we reviewed clinical data and renal biopsies from 22 NIDDM patients to identify important features that would discriminate between DN and NDRD.

MATERIALS AND METHODS

A total of 475 renal biopsy specimens were obtained in the Wonju Christian Hospital from May

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1992 to June 1998. Twenty-six diabetic patients were included in this patient population. The renal biopsy was considered necessary in diabetic patients with (1) a nephritic syndrome or unexplained hematuria; (2) clinically significant proteinuria, occasionally occurring abruptly, or in the absence of retinopathy; (3) rapidly progressive renal failure; or (4) unexplained renal failure with normal-sized kidneys. Of 26 diabetic patients, we excluded patients with malignant tumor and secondary diabetes mellitus (DM), that is, liver disease, pancreatic disease and drug-induced diabetes. NIDDM was defined as basal C-peptide $\geq$ 0.33 nM/L, age at onset of diabetes $\geq$ 30 years and no history of diabetic ketoacidosis.[6] The patients in this study included 22 patients with primary NIDDM out of the 26 diabetic patients.

The clinical data obtained at the time of the renal biopsy for each of the 22 patients included age, sex, anthropometric data, age at onset of diabetes, duration of diabetes, events and symptoms leading to renal biopsy and blood pressure. Onset of DM was the time when DM was first diagnosed. DM duration was the period between the age of onset and renal biopsy. Diabetic retinopathy was diagnosed on funduscopy by an ophthalmologist based on the presence of background retinopathy (microaneurysms, hemorrhages and soft exudates or hard exudates) with or without proliferative changes. Peripheral neuropathy was diagnosed by nerve conduction studies. Nephrotic syndrome was diagnosed by the presence of edema, heavy proteinuria (at least 3.5 g/24 hours), together with a serum albumin $<$3.0 g/dL. Hypertension was diagnosed when sequential diastolic blood pressure readings were 90 mmHg or higher, or when systolic blood pressure readings were $\geq$140 mmHg.[7] Laboratory studies included blood urea nitrogen (BUN), creatinine, fasting and postprandial 2-hour blood glucose, glycated hemoglobin (HbA1c), serum IgG, IgA, IgM and IgE levels, urinalysis with microscopy, 24-hour proteinuria and albuminuria, creatinine clearance and serum complement level. Hematuria was defined as $>$10 red blood cells/L on phase contrast microscopy. If more than 80% of cells in a specimen showed the morphological appearances described by Fairley and Birch, it was recorded as dysmorphic.[8,9] Midstream urine samples were examined within 1 hour.

Biopsy specimens were processed by standard methods. Examination of the kidney biopsy tissue was by light microscopy (hematoxylin-eosin, periodic acid-methenamine silver and periodic acid-schiff staining), immunofluorescence microscopy (antibodies to IgG, IgA, IgM, C1q, C3 and fibrinogen) and electron microscopy. DN was diagnosed by the presence of mesangial expansion, with or without the nodular Kimmelstiel-Wilson formation, basement membrane thickening, fibrin caps or capsular drops. NDRD was categorized following orthodox pathological criteria.[10]

Statistical analysis

Data are expressed as mean$\pm$SD. Differences between groups were assessed by nonparametric statistical tests: Mann-Whitney test, chi-square test, and logistic regression analysis.

RESULTS

Patient profile at renal biopsy

There were a total of 22 patients in the study. All patients were Korean. There were 8 women and 14 men ranging in age from 33 to 68 (51.2$\pm$10.7) years. Their age at the onset of diabetes mellitus ranged from 32 to 66 (46.9$\pm$11.4) years. The duration of diabetes at biopsy ranged from 0 to 13 (4.2$\pm$4.2) years. The serum creatinine at biopsy ranged from 0.6 to 6.6 (1.6$\pm$1.3) mg/dL. Unex-

Table 1. Baseline Characteristics of Non-diabetic Renal Disease (NDRD) and Diabetic Nephropathy (DN) Patients at Renal Biopsy

	NDRD	DN	p
Number of patients	14	8	
Age	51.0$\pm$11.4	51.6$\pm$9.9	NS
Sex (M/F)	8/6	6/2	NS
Body mass index (kg/m^2)	24.8$\pm$4.3	25.1$\pm$2.3	NS
Onset of DM (years)	48.2$\pm$11.8	44.8$\pm$11.1	NS
Duration of DM (years)	2.5$\pm$3.2	7.0$\pm$4.4	$<$0.05
Systolic BP (mmHg)	137.9$\pm$15.8	158.8$\pm$30.9	NS
Diastolic BP (mmHg)	89.3$\pm$12.1	98.8$\pm$12.7	NS
Hypertension	9/14 (64.3%)	5/8 (62.5%)	NS
Smoking	5/13 (38.5%)	5/7 (71.4%)	NS

Data are expressed as mean$\pm$SD.

plained renal failure (serum creatinine >1.5 mg/dL) was observed in 6 patients. Nephrotic syndrome was present in 13 patients.

Fourteen patients were diagnosed as NDRD, 11 had NDRD alone and 3 had NDRD combined with DN, and 8 with isolated DN. The mean duration of DM was significantly shorter in the NDRD patients when compared to the patients with DN (2.5 ± 3.2 vs. 7.0 ± 4.4 years, $p<0.05$). The age, onset of DM, body mass index, systolic and diastolic blood pressure and history of smoking were all similar for the 2 groups (p=N.S., respectively) (Table 1).

Table 2. Biochemical and Clinical Parameters of Non-diabetic Renal Disease (NDRD) and Diabetic Nephropathy (DN) Patients

	NDRD	DN	p
BUN (mg/dL)	26.7±29.0	27.7±11.1	NS
Serum creatinine (mg/dL)	1.5±1.6	1.7±0.7	NS
Serum albumin (g/dL)	3.2±0.9	2.9±1.0	NS
IgG (g/L)	1091.8±597.5	835.8±300.6	NS
IgA (g/L)	328.4±165.7	294.8±93.8	NS
IgM (g/L)	153.2±98.1	133.6±71.6	NS
IgE (g/L)	1028.5±1441.2	334.0±391.0	NS
Fasting glucose (mg/dL)	156.0±62.3	200.7±63.2	NS
HbA1c (%)	7.1±2.3	9.0±3.7	NS
Cholesterol (mg/dL)	268.8±109.0	355.6±169.6	NS
Triglyceride (mg/dL)	286.8±178.0	413.9±411.3	NS
C3 (mg/dL)	117.8±32.2	135.8±31.5	NS
C4 (mg/dL)	30.1±13.3	38.7±17.8	NS
Serum creatinine >1.5 mg/dL	4/14 (28.6%)	2/8 (25.0%)	NS
HbA1c$\leq$9%	11/12 (91.7%)	4/8 (50.0%)	<0.05
Proteinuria (g/24 hours)	3.1±3.3	5.5±2.8	NS
Albuminuria (g/24 hours)	1.7±1.7	4.6±3.5	NS
Creatinine clearance (mL/min)	60.6±31.6	39.3±23.6	NS
Microscopic hematuria	12/13 (92.9%)	6/8 (75.0%)	NS
Proteinuria >3.5 g/24 hours	7/14 (50.0%)	6/8 (75.0%)	NS
Dysmorphic RBC	5/5 (100.0%)	1/3 (33.3%)	<0.05
Retinopathy	1/8 (12.5%)	5/7 (71.4%)	<0.05

Data are expressed as mean±SD.

Associated factors with non-diabetic renal diseases

Looking at the different biochemical and clinical parameters, we found no difference between NDRD and DN patients with regard to BUN, serum creatinine, serum albumin, fasting and postprandial 2-hour glucose, HbA1c, IgG, IgA, IgM, IgE, C3, C4 levels, cholesterol, triglyceride, 24-hour proteinuria, albuminuria, creatinine clearance and incidence of microscopic hematuria. We also looked at the various complications related to long-standing diabetes but found no difference in the incidences of peripheral polyneuropathy or hypertension (Table 2). Significant factors differentiating the 2 groups included the short duration of DM, presence of dysmorphic red blood cells in the urine, absence of retinopathy and HbA1c below 9% ($p<0.05$, respectively, Tables 1 and 2). Multiple logistic regression analysis revealed that the short duration of DM and the absence of retinopathy were factors significantly associated with NDRD.

Non-diabetic renal diseases

The renal pathologic findings are described in Table 3. Isolated DN was seen in 8 patients, 11 had only NDRD and 3 had NDRD (IgA nephropathy, minimal change disease and acute interstitial nephritis) superimposed on DN. Among the 14 patients found to have NDRD, 6 (42.8%) patients had IgA nephropathy, 3 (21.4%) had membranous nephropathy, 3 (21.4%) had minimal change disease, 1

Table 3. Histologic Diagnoses of 22 Biopsies from Patients with Non-insulin Dependent Diabetes Mellitus

Pathologic diagnoses	Number of cases
Non-diabetic renal diseases	14 (63.6%)
IgA nephropathy	6*
Membranous nephropathy	3
Minimal change disease	3*
Lupus nephritis	1
Acute interstitial nephritis	1*
Isolated diabetic changes	8 (36.4%)
Total	22 (100%)

*A total of three cases of non-diabetic renal disease (1 IgA nephropathy, 1 minimal change disease, 1 acute interstitial nephritis) were combined with the diabetic nephropathy.

(7.2%) had membranous lupus nephritis (WHO type V) and 1 (7.2%) had acute interstitial nephritis (Table 3). Histologic changes of DN of variable severity were present in eleven patients (isolated DN and combined with NDRD). Nine biopsy specimens exhibited the features of mixed diffuse and nodular diabetic glomerulosclerosis, 2 exhibited features of only mesangial widening and the thickening of glomerular basement membrane.

DISCUSSION

About 10−35% of patients suffering from NIDDM eventually develop DN over the course of several years which progresses towards end stage renal disease.[11-13] Recently, there have been several reports in the medical literature of non-diabetic, sometimes treatable, renal diseases in patients with NIDDM. The prevalence of NDRD in patients with NIDDM is not well known. Biopsy studies suggest that 25−50% of patients with NIDDM have glomerular lesions unrelated to or in addition to DN.[14-16] However, recruitment bias and lack of uniform criteria for biopsy interpretation may have overestimated NDRD in NIDDM, and superimposed glomerulonephritis in NIDDM is not frequently found in systematic postmortem or biopsy studies.[17,18] From a review of the relevant literature, most of which consists of isolated case reports, it appears that a wide spectrum of NDRD can occur in patients with NIDDM.[19-27] The detection of NDRD in diabetic patients has obvious prognostic and therapeutic importance. Therefore we performed this study to evaluate the factors clinically associated with NDRD in patients with NIDDM. This study was based on the biopsy of 22 diabetics performed because of atypical clinical manifestations and it represents a retrospective analysis of a selected group of patients. Thus, the true incidence of NDRD in NIDDM cannot be deduced from this study as this would require biopsies in all diabetic patients with nephropathy. When considering all 22 patients, 3 (13.6%) were found to have NDRD with DN and 11 (50.0%) with isolated NDRD.

NDRD may be clinically obvious or present merely as a urinary abnormality. The urinary abnormalities such as hematuria in the absence of urinary tract infection or red blood cell casts were clues of NDRD in patients with NIDDM. Although in the report of O'Neill,[19] 5 patients were found to have red blood cell casts in the presence of DN as the sole indicator of renal disease, most other reports,[28,29] and in our opinion also, the occurrence of red blood cell casts and dysmorphic red blood cells in urine are unusual in DN and require further evaluation.

Ninety to 95% of IDDM patients with DN have retinopathy and 40−75% of NIDDM patients with DN have retinopathy.[4,5,14,15] Therefore, the absence of retinopathy seemed to be a useful index in identifying NDRD.[15,30-32] Normal funduscopic findings were also of great value in detecting NDRD in NIDDM patients in this study.

Hyperglycemia appears to be important for the development of proteinuria in NIDDM. Ballard et al. highlighted this association using a proportional hazards analysis to define significant predictors of proteinuria in NIDDM patients.[11] Further normoglycemia with intensive insulin therapy or oral hypoglycemic agents in NIDDM appears to reduce or retard the development of proteinuria.[29,33] Though the level of glucose was similar in both groups in this study, the NDRD group had more patients with satisfactory (HbA1c$\leq$9%) glycemic control ($p<0.05$).

The known duration of diabetes did not accurately predict the presence or severity of DN in NIDDM.[34] But, in some patients, the appearance of significant proteinuria earlier than expected served as a clue to the possible presence of NDRD.[15,31] As shown in this study, therefore, superimposed NDRD should be examined by renal biopsy, particularly if the patient with persistent proteinuria has had diabetes for a short period (less than 5 years) and has no retinopathy.

In previous reports, deterioration of renal function either earlier in the course of diabetes or at a more accelerated pace, such as a decline in glomerular filtration rate exceeding 1 ml/min/momth,[35,36] should also arouse suspicion of NDRD. But in our study, unexplained renal failure was observed in 6 patients, 2 with DN alone, 2 with NDRD alone, and 2 with NDRD with DN. Therefore, unexplained renal failure was the poorest predictor of NDRD, probably because of the difficulty in estimating the exact duration of NIDDM in a population where regular health check-ups rarely take place. In fact, many of these patients had advanced diabetic renal disease, presumably of a longer duration than the known history of diabetes.

Other systemic manifestations or laboratory findings were also helpful. Depending on the individual patient, appropriate screening laboratory tests may reveal hitherto unsuspected autoimmune disorders such as systemic lupus erythematosus.[28] In one of our cases, a 33-year-old female patient had been diagnosed when lupus nephritis presented with malar rash, fever, rheumatoid factor (+), anti-Sm antibody (+) and anti-nuclear antibody (+).

Olivero and Suki reported that 2 out of 3 diabetics with acute glomerulonephritis show spontaneous remission, while the remaining 1 proves to have rapidly progressive glomerulonephritis.[20] Venkateswara and Crosson suggest that the complication of membranous nephropathy in patients with DN may aggravate renal dysfunction requiring early dialysis or renal transplant.[21] The effect of NDRD on prognosis depends on the nature of that lesion and the time of its occurrence in the natural history of the DN. There are, however, no large series studies concerning the effects of the coexistence of superimposed NDRD on the long-term prognosis in diabetic patients. Because some of these disorders can alter the management and prognosis of renal disease in diabetic patients, the appearance of urinary abnormalities or deterioration in renal function inconsistent with the natural history of DN raise the possibility of NDRD and should lead to a more detailed evaluation. The discovery of NDRD in a patient with NIDDM may alter the therapy for renal disease. For instance, diagnosis of certain forms of lupus nephritis, minimal change disease, and, in the opinion of some investigators,[37] idiopathic membranous nephropathy, would call for therapy with immunosuppressive agents. Carstens et al.[22] described the beneficial effect of aggressive therapy in 2 patients with rapidly progressive glomerulonephritis superimposed on DN. In addition, the diagnosis of idiopathic membranous nephropathy mandates a search for possible occult malignancy.[38] We also found a beneficial effect of steroid or cyclophosphamide therapies in 5 patients with NDRD (minimal change disease, membranous nephropathy, lupus nephritis, IgA nephropathy).

We encountered 14 cases of NDRD in 22 NIDDM patients in whom kidney tissue was examined by renal biopsy. Histological examinations demonstrated that NDRD accounted for approximately two-thirds of all our cases. These patients were characterized clinically by a lack of retinopathy, short duration of diabetes and dysmorphic red blood cells in the urine under stable glycemic control. Multiple logistic regression analysis revealed that a short duration of DM and absence of retinopathy were factors significantly associated with NDRD. Although our sample size was small and a selection bias was present in our study, we found that when there is a short duration of DM, or an absence of retinopathy seen in patients with NIDDM, a thorough clinical assessment including repeated urinalysis, laboratory tests, and in selected cases, renal biopsy in diabetic patients aids in the detection of NDRD, some of which may be amenable to treatment.

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