

RENAL HISTOLOGY IN TYPE 2 DIABETES MELLITUS: CLINICOPATHOLOGIC CORRELATION IN 301 PATIENTS

MASAO KANAUCHI, YASUHIRO AKAI, MASAYUKI IWANO,
HIDEO SHIIKI and TOSHIO HASHIMOTO

First Department of Internal Medicine, Nara Medical University

Received October 10, 2001

Abstract : Renal pathologic features in type 2 diabetes and their correlation with clinical manifestations are incompletely known. Renal biopsy specimens from 301 patients were analyzed retrospectively. Light microscopic findings were graded by Gellman's criteria for diffuse glomerular lesions, which included 44 cases in grade D0, 81 in D1, 98 in D2, 49 in D3, and 29 in D4. Amounts of albuminuria or proteinuria correlated significantly with the grade of diffuse glomerular lesions, as did serum creatinine concentration. Creatinine clearance decreased significantly with increasing severity of glomerular lesions. This evidence strongly supports a close relationship between structural changes and functional abnormalities in diabetic nephropathy.

Key words : diabetic nephropathy, proteinuria, renal biopsy, urinary albumin

INTRODUCTION

Diabetic nephropathy has become the most important cause of end-stage renal disease in Japan¹⁾. Declining renal function with increasing albumin or protein excretion are characteristic of diabetic nephropathy²⁾. However, most studies in Western countries have concentrated on structure-function relationships in type 1 diabetes³⁻⁵⁾, and the nature of renal lesions in type 2 diabetes has been a subject of controversy⁶⁻⁸⁾. We report the results of clinicopathologic correlation in over 300 cases of type 2 diabetes followed up at a single institution.

PATIENTS AND METHODS

Patients

Three hundred one patients with type 2 diabetes who underwent renal biopsy at the First Department of Internal Medicine of Nara Medical University Hospital between 1981 and 2000 were included in this review of clinical features and renal histopathology. Indications for renal biopsy in patients studied were significant albuminuria or proteinuria, hematuria, abnormal urinary sediment, or undiagnosed renal dysfunction. Patients with nondiabetic glomerular diseases and urinary tract infection were excluded from the study. We explained the purpose, procedures, possible consequences and complications to each patient prior to renal biopsy, and then obtained written consent.

Clinical assessment and laboratory studies

Hypertension was defined as a systolic blood pressure ≥ 140 mmHg, a diastolic blood pressure ≥ 90 mmHg⁹⁾, or current antihypertensive therapy. Diabetic retinopathy was

assessed by examination of fundus photographs. Hematuria was defined as a Hematest dipstick reading of 1+ or more during routine urinalysis. Serum creatinine was measured by an autoanalyzer, and creatinine clearance was calculated by the Cockcroft-Gault formula¹⁰. Renal dysfunction was assumed when creatinine clearance was < 70 mL/min.

Urine was collected for 24 hr to measure excretion of albumin or protein. At our institution, measurement of "microalbuminuria" was introduced in 1987. For patients admitted between 1981 and 1986, urinary protein concentration was measured by a dye-binding method; for patients admitted after 1987, urinary albumin concentration was measured with an enzyme-linked immunosorbent assay. Accordingly, four grades of urinary albumin / protein excretion were defined: microproteinuria (for patients admitted between 1981 and 1986; urine protein under 0.5 g 24 h⁻¹); normoalbuminuria (for patients admitted after 1987; urine albumin under 30 mg 24 h⁻¹); microalbuminuria (for patients admitted after 1987; urine albumin 30 to 300 mg 24 h⁻¹); and overt proteinuria (urine protein over 0.5 g or urine albumin over 300 mg 24 h⁻¹).

Classification of renal lesions

Tissue specimens obtained by percutaneous renal biopsy were processed for morphometric evaluation by light microscopy. A portion of each specimen was fixed and embedded in paraffin using routine methods. Serial sections 3 μ m thick were cut, and were stained by the periodic acid-Schiff method. Severity of diffuse glomerular changes was graded on a scale of D0 through D4 according to Gellman's criteria¹¹ as follows: D0 (all glomeruli appearing normal); D1 (focal lesion present within each glomerulus, or lesion present focally within the kidney); D2 (mesangial thickening present diffusely within the glomerulus, generalized throughout the kidney); D3 (capillary lumina narrowed and obliterated only focally); and D4 (lumens diffusely narrowed, with the entire glomerulus appearing hyalinized). Nodular lesions also were evaluated by Gellman's criteria¹¹.

Statistical analysis

Statistical analysis was performed by analysis of variance (ANOVA) followed by Scheffe's test, the chi-squared method, and determination of Spearman's correlation coefficient. P values below 0.05 were considered to indicate statistical significance.

RESULTS

Diffuse glomerular lesions were graded as D0 in 44 cases (14.6%), D1 in 81 cases (26.9%), D2 in 98 cases (32.6%), D3 in 49 cases (16.3%), and D4 in 29 cases (9.6%). Nodular lesions were observed in 8.2% of D2 cases, 69.4% in D3, and 96.5% in D4, but not in D0 and D1. Clinical and laboratory features corresponding to each grade of diffuse glomerular lesion are summarized in Table 1. Patients with more advanced lesions were more likely to have had a longer duration of diabetes than those with mild lesions ($r=0.439$, $p<0.001$). Patients with more advanced lesions also were more likely to have hypertension ($\chi^2=22.4$, $p<0.001$) and retinopathy ($\chi^2=86.3$, $p<0.001$). The prevalence of hematuria increased significantly as severity of glomerular lesions worsened ($\chi^2=64.7$, $p<0.001$). Mean serum creatinine showed a significant increase ($r=0.388$, $p<0.001$), while creatinine clearance decreased ($r=-0.338$,

Table 1. Clinicopathologic correlation

	All patients	Diabetic glomerulopathy					Statistical significance
		D0	D1	D2	D3	D4	
n	301	44	81	98	49	29	-
Male/Female	189/112	24/20	51/30	65/33	27/22	22/7	-
Age (yrs)	56.9 ± 9.7	52.3 ± 9.5	56.7 ± 9.3	59.0 ± 10.1	56.5 ± 9.6	58.4 ± 8.1	ns
Diabetes duration(yrs)	8.9 ± 6.9	3.7 ± 3.3	7.3 ± 6.7	9.3 ± 6.3	12.5 ± 6.5	13.8 ± 7.3	<0.001 ¶
Hypertension(%)	40.2	36.4	27.2	38.8	46.9	75.9	<0.001 †
Retinopathy(%)	43.6	12.2	20.2	43.3	80.9	92.6	<0.001 †
Hematuria(%)	21.3	5.0	8.1	15.7	37.2	74.1	<0.001 †
Serum creatinine (mg/dL)	0.82 ± 0.38	0.69 ± 0.16	0.69 ± 0.19	0.80 ± 0.37	0.94 ± 0.45	1.23 ± 0.55	<0.001 ¶
Creatinine clearance (mL/min)	91 ± 37	105 ± 35	101 ± 34	91 ± 35	80 ± 40	59 ± 21	<0.001 ¶
Renal dysfunction(%)	32.6	11.4	21.2	31.2	46.9	78.6	<0.001 †

Data are number of patients, percentages, or mean ± SD.

¶, Spearman's correlation coefficient; †, chi-square test.

Table 2. Degree of albuminuria / proteinuria for different grades of diffuse glomerular lesions

	All patients	Diabetic glomerulopathy					Statistical significance
		D0	D1	D2	D3	D4	
1981-1986] <0.001]
microproteinuria	61	25	21	12	3	0	
1987-2000							
normoalbuminuria	117	16	44	57	0	0	
microalbuminuria	49	3	14	20	12	0	
1981-2000							
overt proteinuria	74	0	2	9	34	29	

p<0.001) with progression of glomerular lesions. The prevalence of renal dysfunction paralleled severity of glomerular lesions ($\chi^2=196.1$, p<0.001). Degree of albuminuria / proteinuria was significantly associated with progression of diffuse glomerular lesions ($\chi^2=171.2$, p<0.001 among normoalbuminuria, microalbuminuria, and overt proteinuria; $\chi^2=242.6$, p<0.001 including microproteinuria; Table 2).

DISCUSSION

Clinicopathologic analyses of diabetic nephropathy have been reported mostly in cases of type 1 diabetes³⁻⁵⁾ but these relationships have not been well defined in patients with type 2 diabetes, the most common type of diabetes in Japan. Inomata et al.⁶⁾ examined renal biopsy

specimens in 27 patients with type 2 diabetes and concluded that persistent microalbuminuria usually is accompanied by relatively advanced renal lesions, graded as D2 or D3. Otherwise, the normoalbuminuric and microalbuminuric patients showed similar clinical parameters such as age, duration of diabetes, HbA1, and creatinine clearance, while differing in frequency of proliferative retinopathy. Suzuki et al.⁷⁾ studied relationships between diabetic renal lesions and clinical features in 108 patients with type 2 diabetes, and demonstrated that the severity of glomerular lesions had a significant positive correlation with urinary protein excretion and a negative correlation with glomerular filtration rate. In 21 type 2 diabetic patients, White and Bilous⁸⁾ noted that increased mesangial volume (indicating severity of diffuse glomerular lesions) was associated with more marked proteinuria and low creatinine clearance. In the present study, we closely examined the relationship between structure and function in a larger group of 301 patients with type 2 diabetes. We observed that the degree of albuminuria/proteinuria was correlated significantly with progression of diffuse glomerular lesions; mean serum creatinine significantly increased and creatinine clearance significantly decreased with increasing severity of glomerular lesions. This evidence strongly supports a close relationship between structure and function in nephropathy in type 2 diabetic patients.

REFERENCES

- 1) Kikkawa, R., Kida, Y. and Haneda, M. : Nephropathy in type 2 diabetes. Epidemiological issues as viewed from Japan. *Nephrol. Dial. Transplant.* **13**: 2743-2745, 1988.
- 2) Mogensen, C. E., Christensen, C. K. and Vittinghus, E. : The stages in diabetic renal disease. *Diabetes* **32** (Suppl.2): 64-78, 1983.
- 3) Mauer, S. M., Steffes, M. W., Ellis, E. N., Sutherland, D. E. R., Brown, D. M. and Goetz, F. C. : Structural-functional relationships in diabetic nephropathy. *J. Clin. Invest.* **74**: 1143-1155, 1984.
- 4) Chavers, B. M., Bilous, R. W., Ellis, E. N., Steffes, M. W. and Mauer, S. M. : Glomerular lesions and urinary albumin excretion in type 1 diabetes without overt proteinuria. *N. Engl. J. Med.* **320**: 966-970, 1989.
- 5) Lane, P. H., Steffes, M. W. and Mauer, S. M. : Glomerular structure in IDDM women with low glomerular filtration rate and normal urinary albumin excretion. *Diabetes* **41**: 581-586, 1992.
- 6) Inomata, S., Nakamoto, Y., Inoue, M., Itoh, M., Ohsawa, Y. and Masamune, O. : Relationship between urinary albumin excretion rate and renal histology in non-insulin-dependent diabetes mellitus; with reference to the clinical significance of microalbuminuria. *J. Diabetic Compl.* **3** : 172-178, 1989.
- 7) Suzuki, Y., Ueno, M., Hayashi, H., Satou, H., Karasawa, R., Inn, H., Suzuki, S., Maruyama, Y. and Arakawa, M. : A light microscopic study of glomerulosclerosis in Japanese patients with non-insulin-dependent diabetes mellitus. *Clin. Nephrol.* **42** : 155-162, 1994.
- 8) White, K. E. and Bilous, R. W. : Type 2 diabetic patients with nephropathy show structural-functional relationships that are similar to type 1 disease. *J. Am. Soc. Nephrol.* **11** : 1667-1673, 2000.
- 9) 1999 World Health Organization-International Society of Hypertension Guidelines for Management of Hypertension. *J. Hypertens* **17** : 151-183, 1999.
- 10) Cockcroft, D. W. and Gault, M. H. : Prediction of creatinine clearance from serum creatinine. *Nephron* **16**: 31-41, 1976.
- 11) Gellman, D. D., Pirani, C. L., Soothill, J. F., Muehrcke, R. C. and Kark, R. M. : Diabetic nephropathy; a clinical and pathologic study based on renal biopsies. *Medicine* **38** : 312-367, 1959.