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Renal outcomes in patients with type 2 diabetes with or without coexisting non-diabetic renal disease

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ABSTRACT

Aims: We sought not only to determine the independent predictors of non-diabetic renal disease (NDRD) but also to investigate the impact of NDRD on renal outcomes in patients with type 2 diabetes who underwent renal biopsy and were followed-up longitudinally.
Methods: The present study was conducted by reviewing the medical records of 119 type 2 diabetic patients who underwent renal biopsy at Yonsei University Health System from January 1988 to December 2008.
Results: Renal biopsy findings declared that 43 patients (36.1%) had diabetic nephropathy alone, 12 (10.1%) had NDRD superimposed on diabetic nephropathy, and 64 (53.8%) had only NDRD. On multivariate analysis, the absence of diabetic retinopathy, higher hemoglobin levels, and shorter duration of diabetes were independent predictors of NDRD in these patients. During the follow-up period, end-stage renal disease (ESRD) developed in 33 patients (27.7%). On multivariate Cox regression, higher serum creatinine levels, higher systolic blood pressure, longer duration of diabetes, and the presence of diabetic nephropathy were identified as significant independent predictors of ESRD. When the presence of diabetic retinopathy was included in the multivariate model, higher serum creatinine levels, higher systolic blood pressure, and the presence of retinopathy were shown to be independent predictors of ESRD.
Conclusions: Since diabetic patients with NDRD have significantly better renal outcomes compared to patients with biopsy-proven diabetic nephropathy, it is important to suspect, identify, and manage NDRD as early as possible, especially in type 2 diabetic patients with short duration of diabetes and those without diabetic retinopathy or anemia.

1. Introduction

Diabetic nephropathy is the leading cause of end-stage renal disease (ESRD) worldwide, and its prevalence is strikingly rising mainly due to a recent significant increase in the number of type 2 diabetic patients [1]. Even though diabetic nephropathy is rarely diagnosed by renal biopsy in patients with diabetes of short duration, the diagnosis is usually made based on clinical features in the context of longstanding diabetes mellitus with target organ damage, such as retinop-

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athy or neuropathy, and proteinuria preceding azotemia. This kind of clinical approach has clearly been validated in patients with type 1 diabetes, but has not been as well verified in type 2 diabetic patients. In patients with type 1 diabetes of more than 10 years, especially when diabetic retinopathy or neuropathy is accompanied, proteinuria is usually a manifestation of diabetic nephropathy, which is histologically proven in >95% of patients [2–4]. In these patients, therefore, renal biopsy is not mandatory for diagnosis. However, in type 2 diabetic patients, a more heterogeneous pattern of renal lesions has been demonstrated, suggesting that a possibility of non-diabetic renal diseases (NDRD) should always be considered in patients with type 2 diabetes [5]. Reports on the prevalence of NDRD in type 2 diabetic patients have varied widely from 12 to 81% [6–18]. This variation may be due to the fact that most of the NDRD in type 2 diabetic patients has been diagnosed by renal biopsy based on variety of indications.

On the other hand, it is well known that the pathological changes of diabetic nephropathy are almost always irreversible, while some forms of NDRD, such as minimal change disease, membranous nephropathy, and acute interstitial nephritis, are often treatable or even remittable [19]. Since the treatment and prognosis of diabetic nephropathy and NDRD are quite different, discernment of NDRD from diabetic nephropathy is of considerable importance. Previous studies have revealed several conducive clinical and laboratory findings that can be used to discriminate between the two [6–18]. Nevertheless, the results were not uniform, likely due to differences in the study populations and selection criteria. Moreover, the influence of NDRD on renal outcomes in type 2 diabetic patients has not been well established, and most of the available data have been retrieved from cross-sectional studies [20–25]. In this study, therefore, we not only sought to determine the independent predictors of NDRD but also to investigate the impact of NDRD on renal outcomes in patients with type 2 diabetes who underwent renal biopsy and were followed-up longitudinally.

2. Methods

2.1. Patients

The present study was conducted by reviewing the medical records of 138 type 2 diabetic patients who underwent percutaneous renal biopsy at Yonsei University Health System from January 1988 to December 2008. All patients were diagnosed as type 2 diabetes, as defined by the World Health Organization and the American Diabetes Association, with the absence of ketosis-prone state (absence of significant ketonuria and insulin treatment started at least 1 year after diagnosis) [26,27]. Among the 138 patients, 19 were excluded due to advanced renal failure (serum creatinine $\geq$ 5.0 mg/dl) at the time of biopsy, malignancy, and/or secondary diabetes mellitus, and in the result, the data of the remaining 119 patients were included in our analysis. Biopsy indications were uniform throughout the study, and were based on clinically strong suspicion of NDRD, including rapidly increasing amount of proteinuria or nephrotic syndrome (71 patients, 59.7%), heavy proteinuria or renal insufficiency in conjunction with diabetes of relatively short duration and/or the absence of diabetic retinopathy (27 patients, 22.7%), unexplained impaired or rapidly declining renal function (13 patients, 10.9%), and persistent hematuria of glomerular origin (8 patients, 6.7%). Renal tissue obtained by percutaneous needle biopsy was sent to the pathologist for light, immunofluorescent, and electron microscopic examination. Diabetic nephropathy was diagnosed based on the presence of mesangial expansion and diffuse intercapillary glomerulosclerosis with or without Kimmelstiel–Wilson nodule, basement membrane thickening, and exudative lesions, such as fibrin cap, capsular drop, or hyaline thrombus [28].

The following clinical data were collected for each patient: age at the time of renal biopsy, gender, duration of diabetes prior to biopsy, presence of hypertension, presence of diabetic retinopathy, and history of gross hematuria. The following laboratory data were collected at the time of renal biopsy: urinalysis, hemoglobin, blood urea nitrogen, serum creatinine, serum albumin, total serum cholesterol, fasting blood glucose, hemoglobin $A1_C$ ($HbA1_C$) concentrations, 24-h urinary protein and albumin excretion, and creatinine clearance. Kidney size was defined as the mean of the maximal longitudinal axis of the right and left kidneys on abdominal ultrasonography. Hypertension was defined as systolic blood pressure $\geq$130 mmHg and diastolic blood pressure $\geq$80 mmHg or antihypertensive medications being taken by the patient. Diabetic retinopathy was diagnosed by direct ophthalmoscopy and fluorescence retinography performed by an ophthalmologist. Hematuria was defined as >3 red blood cells per high power field in a centrifuged urine sample.

2.2. Statistical analysis

All values are expressed as mean $\pm$ standard deviation (SD) or percentages. Statistical analyses were performed using SPSS for Windows Ver 13.0 (SPSS, Inc., Chicago, IL, USA). Data were analyzed using Student's *t*-test, chi-square test, or Fisher's exact test, and ANOVA was used for multiple comparisons. Independent predictors of NDRD were determined by logistic regression analysis, including all covariates with a *p*-value of <0.05 on univariate analysis. To identify risk factors for ESRD, which was the end point of this study and was defined as advanced renal failure requiring maintenance dialysis or renal transplantation, multivariate logistic regression analysis and multivariate Cox regression analysis were performed. Kaplan–Meier analysis and log rank test were used to compare the difference in cumulative renal survival according to the risk factors identified on Cox regression analysis. The patients were censored on December 30, 2009, but patients who did not reach this date were administratively censored and designated as the non-ESRD group. A *p*-value less than 0.05 was considered statistically significant.

3. Results

3.1. Patient profiles and pathologic findings

A total of 119 patients with a mean follow-up duration of 40.2 $\pm$ 44.2 months were included in the present study. The mean age of the patients at the time of renal biopsy was 53.1