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Original Investigation

Association of Urinary Type IV Collagen With GFR Decline in Young Patients With Type 1 Diabetes

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Background: Some patients with diabetes have advanced diabetic glomerular lesions and progressive kidney function decline even if urinary albumin levels are in the normal range. Therefore, another prognostic marker for diabetic kidney disease needs to be identified. We aimed to clarify whether urinary type IV collagen is associated with the progression of kidney function decline in patients with type 1 diabetes.

Study Design: Hospital-based observational cohort study.

Setting & Participants: 231 normo- and microalbuminuric patients with type 1 diabetes who were younger than 40 years at the start of the study.

Predictor & Measurements: Urinary type IV collagen, determined using a 1-step sandwich enzyme immunoassay.

Outcome: The primary outcome measurement was rate of change in estimated glomerular filtration rate (eGFR).

Results: Mean follow-up was 7.4 ± 1.3 (standard deviation) years. Urinary type IV collagen-creatinine ratio (T4C) was associated significantly with rate of change in eGFR in both univariate ($r = -0.169$; $P = 0.01$) and multivariate regression analyses (standardized estimate = −0.131; $P = 0.03$). In the sensitivity analysis limited to patients with normoalbuminuria (n = 213), T4C, but not urinary albumin-creatinine ratio (ACR), was associated significantly with rate of change in eGFR (standardized estimate = −0.12; $P = 0.03$). The interaction between logarithmically transformed ACR and logarithmically transformed T4C on eGFR decline was not significant (P for interaction = 0.2). We compared the adjusted rate of change in eGFR among 4 groups classified according to normal or increased T4C and ACR values and found that the rate of decline in eGFR in patients with increased T4C and normal ACR values was significantly faster than that in patients with normal T4C and ACR values (−4.3 and −3.0 mL/min/1.73 m^2/y; $P = 0.004$, analysis of covariance).

Limitations: Study size was relatively small.

Conclusions: T4C is associated with progression of kidney function decline in young patients with type 1 diabetes.

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INDEX WORDS: Urinary type IV collagen; diabetic kidney disease; kidney function decline; albuminuria.

Diabetic kidney disease is a substantial cause of end-stage renal disease worldwide,[1] and the risk of end-stage renal disease in patients with type 1 diabetes is 25%-50% during these individuals' lifetimes.[2,3] Hence, there is an urgent requirement for a prognostic marker for the decrease in kidney function. Such a marker would enable initiation of early intervention. Currently, albuminuria is considered the most sensitive prognostic marker for the progression of diabetic kidney disease.[4,5] However, previous reports have indicated that some patients with normoalbuminuria have advanced diabetic glomerular lesions, decreased glomerular filtration rate (GFR), and progressive kidney function decline.[6,7] Consequently, another prognostic marker for diabetic kidney disease needs to be identified.

Morphologically, diabetic kidney disease is characterized by thickening of the glomerular basement membrane and extracellular matrix expansion surrounding mesangial cells.[8] Type IV collagen is the main component of glomerular basement membrane and mesangial matrix.[9] Urinary type IV collagen is affected minimally by serum levels because of its high molecular weight of ~540 kDa,[10] which is too large for filtration through glomeruli. Therefore, its increased shedding from glomeruli is considered to be responsible for increased urinary type IV collagen levels. Increased urinary type IV collagen levels are associated with decreased kidney function and increased urinary albumin excretion.[11,12] However, previous studies that investigated the relationship be-

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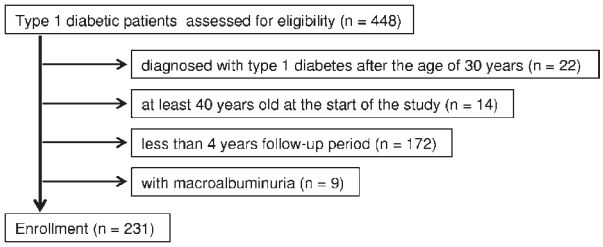

Figure 1. Flow diagram of the study population.

tween urinary type IV collagen levels and decreased kidney function in patients with type 1 diabetes were limited by cross-sectional design. Therefore, we conducted a long follow-up study to determine whether urinary type IV collagen is associated with the kidney function decline in young patients with early-onset type 1 diabetes.

METHODS

Patients

This study included normo- and microalbuminuric patients for whom type 1 diabetes had been diagnosed before the age of 30 years, who had been treated as outpatients at the Diabetes Center, Tokyo Women's Medical University School of Medicine, from 1998-2003, and who were younger than 40 years at the start of observation. Figure 1 shows the composition of the study population. Overall, 231 patients were enrolled.

Baseline Evaluations and Definitions

This study was a hospital-based observational cohort study designed in adherence to the Declaration of Helsinki. Baseline evaluation included measurement of height, weight, blood pressure, hemoglobin A_{1c} (HbA_{1c}), lipid profile, serum creatinine, presence or absence of retinopathy, and use or nonuse of antihypertensive or antilipid drugs. Criteria for type 1 diabetes included clinical features and laboratory data. All patients were prone to ketosis, lacked endogenous insulin secretion (given urinary C-peptide levels <3.3 nmol/d), and required more than 4 insulin injections per day.[13] To assess diabetic retinopathy, funduscopic examinations with dilated pupils were performed by ophthalmologists during the baseline year. Diabetic retinopathy was defined as the presence of microaneurysms or dot hemorrhages or new vessels, vitreous hemorrhage, vitreoretinal traction, or retinal detachment believed to be attributable to diabetic neovascularization.

Measurements

Urinary albumin-creatinine ratio (ACR) and urinary type IV collagen-creatinine ratio (T4C) were measured in first-voided urine samples collected early in the morning on the day of the hospital visit. Urinary albumin was measured using a latex agglutination immunoturbidimetric assay (Eiken Chemical, www.eiken.co.jp) to calculate ACR. Urinary type IV collagen was measured using a 1-step sandwich enzyme immunoassay (urinary type IV collagen assay kit; Daiichi Fine Chemical, www.daiichi-fcj.co.jp) to calculate T4C. Intra-assay coefficients of variation for T4C were 6.78%, 2.56%, and 4.27% with low, midrange, and high levels of T4C, respectively. Interassay coefficients of variation for T4C were 7.42%, 6.45%, and 5.14% with low, midrange, and high levels of T4C, respectively.

Level of T4C was defined as normal T4C (≤4.0 μg/g creatinine[14]), and ACR stages were defined as normo- (ACR <30 mg/g creatinine) or microalbuminuria (ACR ≤30-<300 mg/g creatinine[5]) based on at least 2 of 3 measurements.

Total cholesterol was measured using an enzymatic method. High-performance liquid chromatography (HA8131; Daiichi Kagaku, www.arkray.co.jp) was used to measure HbA_{1c} according to previous Japanese standard substance and measurement methods. This measurement was termed HbA_{1c} (JDS), where JDS stands for Japan Diabetes Society. National Glycohemoglobin Standardization Program–equivalent values were obtained using the equation $HbA_{1c} = HbA_{1c}$ (JDS) + 0.4.[15]

Estimated GFR

GFR for an adult (age ≥18 years) was estimated using the following equation, originating from the Modification of Diet in Renal Disease (MDRD) Study group[16] and refitted for Japanese individuals: estimated GFR (eGFR) = $194 \times \text{SCr (mg/dL)}^{-1.094} \times \text{Age}^{-0.287} \times 0.739$ (if female), where SCr is serum creatinine level.[17] GFR for children (age <18 years) was estimated using the equation: eGFR = Length (cm) × k/SCr (mg/dL), where k = 0.70 for boys 13 years or younger and k = 0.55 for the others.[18]

Serum creatinine was measured using the Jaffé method and calibrated using the following equation ($r = 0.999$; $P < 0.001$)[19]: SCr (enzymatic method) = 0.972 × SCr (Jaffé method) − 0.224.

Outcome Measurement

The primary outcome measurement of this study was rate of change in eGFR. Intraindividual rates were determined using parameter estimates from a simple regression analysis, with eGFR as a function of time in years applied to all eGFR values calculated for the duration of follow-up.

Statistical Analysis

Data were expressed as percentages, arithmetic mean ± standard deviation, or median (25th-75th percentile), as appropriate on the basis of data distribution. Categorical data were compared using Fisher exact probability test, and continuous data were compared using *t* test. Relationships between variables were assessed using Pearson correlational analysis or multivariate linear regression analysis. Analysis of covariance was performed for comparison among the 4 groups. The following covariates were used as conventional risk factors: age, sex, duration of diabetes, presence of retinopathy, eGFR at baseline, and mean values during the follow-up period for HbA_{1c}, systolic blood pressure, body mass index, and total cholesterol. PASW Statistics 18 (SPSS Japan Inc, www.spss.co.jp) and SAS, version 9.2 (SAS Institute, www.sas.com), were used for analysis. $P < 0.05$ is considered significant.

RESULTS

Demographic and Clinical Characteristics

Baseline clinical characteristics and laboratory data are listed in Table 1. We studied 231 patients with type 1 diabetes, including 146 female and 85 male with a mean age of 24 ± 7 (range, 5-39) years. At baseline, 188 patients had T4Cs within normal ranges, and the remaining 43 patients had increased T4Cs. Additionally, 213 patients had normoalbuminuria and 18 had microalbuminuria. T4C was associated significantly with ACR (n = 231; $r = 0.220$; $P = 0.001$). ACR was associated with eGFR ($r = 0.180$; $P = 0.006$), but