Clinical Significance of Urinary Liver-Type Fatty Acid–Binding Protein in Patients With Diabetic Nephropathy

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Tubulointerstitial damage plays a crucial role in the progression of kidney diseases, including diabetic nephropathy (1). Among several distinct types of fatty acid–binding protein (FABP), liver-type FABP (L-FABP) is abundantly expressed in hepatocytes and constitutively expressed in proximal tubular cells of the kidney (2). L-FABP incorporates albumin-bound free fatty acids (FFAs) that are filtered through the glomeruli into proximal tubular cells and transports FFAs from the cytosol to the nucleus (3). In transgenic mice expressing human L-FAPB, protein overload, resulting in massive proteinuria, upregulated renal L-FABP expression and increased its urinary excretion (4), suggesting that urinary L-FABP may reflect tubulointerstitial damage. Recently, in patients with nondiabetic glomerular disease, urinary excretion of L-FABP increased in parallel with the severity of tubulointerstitial injury and correlated with proteinuria and the rate of progression of renal disease, suggesting that L-FABP may be a useful indicator for the progression of nondiabetic kidney disease (4,5). To determine the clinical significance of L-FABP in patients with diabetic nephropathy, we conducted a cross-sectional study comparing urinary L-FABP excretion in diabetic patients with serial stages of kidney disease.

RESEARCH DESIGN AND METHODS

— Adult patients with type 2 diabetes were recruited from the outpatient clinic of the Division of Nephrology and Hypertension, Diabetes Center, Tokyo Women's Medical University Hospital, Tokyo, Japan. Patients were classified into four stages of nephropathy according to albumin-to-creatinine ratio (ACR) in the first-morning urine and serum creatinine concentrations. Patients with a serum creatinine concentration ≥2.0 mg/dl were categorized as having renal failure. Patients with serum creatinine <2.0 mg/dl were classified as normoalbuminuric if ACR was <30 mg/g creatinine, as microalbuminuric if ACR was 30–299 mg/g creatinine, and as having clinical albuminuria if ACR was ≥300 mg/g creatinine (6).

Urinary albumin and L-FABP concentrations were measured by the latex agglutination method (5) and a highly sensitive sandwich enzyme-linked immunosorbent assay (CMIC, Tokyo, Japan). Concentrations were normalized for urine creatinine concentration. Intra- and inter-assay coefficients of variation for the urine L-FABP concentration were 7.0–21.7 and 1.2–7.4%, respectively. The detection limit of L-FABP was 0.15 ng/ml; concentrations below this limit were defined as 0.10 ng/ml. Glomerular filtration rate (GFR) was estimated using the abbreviated equation proposed by the MDRD (Modification of Diet in Renal Disease) study group (7).

Data were expressed as arithmetic mean ± SD or geometric mean (95% CI), as appropriate according to data distribution. Continuous data were compared using one-way ANOVA followed by multiple comparisons by Tukey's Studentized range test; categorical data were analyzed with Cochran-Armitage trend test. For univariate correlation analyses, Spearman's correlation coefficient (*rs*) was calculated. For multiple regression analysis, age, sex, BMI, HbA_{1c} (A1C), urinary albumin excretion, and estimated GFR were included as covariates. All statistical analyses were performed using the SAS (SAS Institute, Cary, NC) version 9.13. $P < 0.05$ was considered significant.

RESULTS

— We studied a total of 356 ambulatory individuals (127 women and 229 men) with type 2 diabetes with a mean ± SD age of 63 ± 11 years (range 31–89). Among these, 216 patients were normoalbuminuric and 64, 46, and 30 patients were classified as microalbuminuric, as having clinical albuminuria, or as having renal failure, respectively. Sex distribution, mean age, and BMI were comparable among the four groups. Patients with more advanced stages of kidney disease were more likely treated with insulin and antihypertensives. For the respective four groups, geometric mean (95% CI) ACR was 7.8 (6.2–9.8), 82.9 (55.2–124.4), 867.3 (634.5–1,185.6), and 1,071.4 (702.5–1,634.1) mg/g creatinine ($P < 0.001$); serum creatinine concentration was 0.94 ± 0.19, 1.07 ± 0.26, 1.29 ± 0.40, and 3.34 ± 1.14 mg/dl ($P < 0.001$); and estimated GFR was 79.0 ± 14.9, 72.3 ± 17.4, 61.2 ± 21.2, and 21.6 ± 8.4 ml · min^{-1} · 1.73 m^{-1} ($P < 0.001$).

Geometric mean (95% CI) urinary L-FABP–to–creatinine ratio was 3.0 (2.4–3.8) μg/g creatinine in normoalbuminuric patients, 5.2 (3.4–7.7) μg/g creatinine in microalbuminuric patients, 31.2 (22.8–

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Received for publication 2 March 2005 and accepted in revised form 15 May 2005.

Abbreviations: ACR, albumin-to-creatinine ratio; FABP, fatty acid–binding protein; FFA, free fatty acid; GFR, glomerular filtration rate; L-FABP, liver-type FABP.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

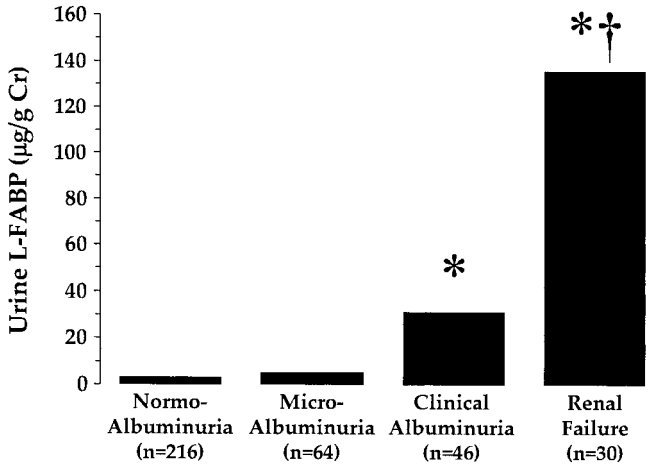

Figure 1—*Comparison of geometric mean of urine L-FABP in diabetic patients with serial stages of kidney disease. *P < 0.001 vs. normoalbuminuria and microalbuminuria, †P < 0.001 vs. clinical albuminuria.*

42.7) μg/g creatinine in patients with clinical albuminuria, and 135.3 (88.7–206.3) μg/g creatinine in patients with renal failure (Fig. 1). In patients with clinical albuminuria and renal failure, urinary L-FABP was significantly increased compared with patients with normo- and microalbuminuria ($P < 0.001$). The difference between patients with clinical albuminuria and renal failure was also statistically significant ($P < 0.001$). In the univariate correlation analyses, urinary albumin was proportionally ($rs = 0.574$, $P < 0.001$) and GFR was inversely ($rs = -0.383$, $P < 0.001$) correlated with urinary L-FABP. No statistical correlation was observed between L-FABP and age or A1C. In the multiple regression analysis, both urinary albumin concentration and GFR, but not other variables, were statistically associated with urinary L-FABP, with parameter estimates ± SE of 0.483 ± 0.050 ($P < 0.001$) for logarithmically transformed urinary albumin and −0.007 ± 0.002 ($P = 0.001$) for GFR.

CONCLUSIONS — We found in this cross-sectional study, a significant association between the stage of diabetic nephropathy and urinary L-FABP. These results are consistent with previous studies (4,5) in patients with nondiabetic glomerular diseases, in which urinary L-FABP was associated with severity of tubulointerstitial injury, proteinuria, and the rate of progression of kidney disease. These findings may implicate a common mechanism of increased urinary L-FABP excretion in the pathogenesis of diabetic and nondiabetic kidney diseases.

In glomerular diseases, whether diabetic or nondiabetic, increased protein filtration through the glomeruli, including cytotoxic cytokines and complement components, causes tubulointerstitial injury (1). In our study, diminished GFR was independently associated with increased urinary L-FABP excretion. Urinary L-FABP also tended to be greater in microalbuminuric than in normoalbuminuric patients, although this difference did not reach statistical significance. These findings suggest that urinary L-FABP may be associated with advanced kidney disease in diabetes.

In conclusion, we found a close association of urinary L-FABP excretion with advanced diabetic nephropathy in patients with type 2 diabetes. Significance of urinary L-FABP in assessing the effects of glycemia, diabetes medications, and blood pressure control upon tubular/interstitial health remains to be tested. In addition, the prognostic value of urinary L-FABP in the progression of diabetic kidney disease should be determined prospectively.

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