Urinary liver-type fatty acid binding protein and chronic kidney disease

The number of the dialysis patient increases year by year, with diabetic kidney disease as the main contributor. Therefore, diagnostic markers for predicting the prognosis of early diabetic kidney disease are needed to distinguish patients who are at higher risk of progression to ESRD, start renal protective therapy, and thus decrease the number of patients with ESRD.

Urinary albumin has been used not only for diagnosis and categorization of diabetic kidney disease, but also in the evaluation of management strategies. However, several studies showed un-coupling of the development of increased urinary albumin levels and the occurrence of renal dysfunction. Krolewski *et al*. described normoalbuminuria patients with a baseline glomerular filtration rate over 105 who had early progressive renal dysfunction,[1] indicating that more reliable biomarkers are necessary.

In addition to the glomerular changes, tubulointerstitial injury has an important impact on the progression of diabetic kidney disease. Tubular biomarkers may reflect pathophysiological conditions that cannot be detected by measuring urinary albumin. Liver-type fatty-acid binding protein (L-FABP) is expressed in the proximal tubules of the human kidney and participates in fatty acid metabolism. Free fatty acids (FFAs) are bound to albumin, filtered through the glomeruli, and reabsorbed into the proximal tubules. FFAs loaded on the proximal tubules are then bound to L-FABP and transported to mitochondria or peroxisomes, where they are metabolized by β-oxidization.[2]

In order to evaluate the dynamics of human L-FABP in kidney disease, transgenic animal model studies were performed.[3] Human L-FABP gene expression in the kidney was found to be up-regulated and urinary excretion of human L-FABP was increased by stress, such as urinary protein overload, tubular stretch, hypertension, ischemia-reperfusion, and toxins that cause tubulointerstitial damage.[3] We speculate that increased urinary L-FABP levels in humans result from up-regulation of L-FABP gene expression in the kidney.

The present study[4] is the first to show clinical significance of increased urinary L-FABP during progression of diabetic kidney disease in Indian patients with type 2 diabetes. Urinary L-FABP levels were also higher in normoalbuminuric patients than in control subjects. Similar results were reported in studies of Japanese and European populations.[5,6] In a prospective observational follow-up study of type 1 or type 2 diabetic patients, increased urinary L-FABP levels were found to be associated with progression of diabetic kidney disease.[5,7] These results indicated that urinary L-FABP levels accurately reflected the disease severity and could potentially serve as a clinical marker to identify patients who are likely to experience disease progression. Furthermore, there have been numerous reports of intervention studies in which urinary L-FABP levels correlate with responses to renoprotective treatment.[8] Based on these results, a urinary human L-FABP ELISA kit developed by CMIC Holdings Co. Ltd. (Tokyo, Japan) was authorized as an extracorporeal diagnostic agent, and urinary L-FABP was approved as a tubular injury biomarker in clinical practice by the Ministry of Health, Labour and Welfare in Japan in 2011.[8] Unfortunately, the urinary L-FAB*P* values in this Indian study were measured using a "research use only" diagnostic kit.

Long-term observational studies of type 2 diabetes patients with normoalbuminuria and microalbuminuria have been performed with about 12 years of follow-up.[9] Araki *et al*. reported recently that increased urinary L-FABP levels were associated with the occurrence of future cardiovascular events, in addition to progression to ESRD, and even in patients with normalbuminuria.[9] Urinary L-FABP may reflect the degree of systemic microcirculation injury and thus be a predictive marker for the onset of cardiovascular disease. A longitudinal study using an authorized urinary human L-FABP ELISA kit with confirmed accuracy is needed to reveal correlations between urinary L-FABP and renal prognosis or the onset of cardiovascular events in Indian subjects with type 2 diabetes.

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