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COMMENTARY

Urinary adiponectin and progression of diabetic nephropathy in type 1 diabetes

Diabetic nephropathy (DN) affects 30% of all type 1 diabetic patients. It is characterized by morphological and ultrastructural changes in the kidney, including deposition of extracellular matrix and thickening of the glomerular basement membrane. DN is a major public health concern, as it is associated with the deterioration of renal function, eventually resulting in end-stage renal disease (ESRD), as well as a high risk of cardiovascular disease and premature death. Thus, early screening is important for preventing disease deterioration. Generally, monitoring of adaptable biomarkers, such as albumin excretion rate (AER) or estimated glomerular filtration rate (eGFR), for DN screening is indicated. However, there are major limitations to these tests in patients with advanced DN, as they have high interindividual variability[1]. In addition, Perkins *et al.*[2] reported that 50% of patients with type 1 diabetes showed renal disease progression in the absence of overt albuminuria. Furthermore, an association between reduced glomerular filtration rate and DN was only present during the late stages of the disease[3]. Thus, new biomarkers are required for the early and accurate detection of DN.

Adiponectin, an adipocyte-derived vasoactive peptide, has anti-inflammatory and insulin-sensitizing properties, as well as cardioprotective effects on endothelial cells. Previous studies have established an association between adiponectin levels and metabolic disorders, such as obesity and diabetes mellitus; furthermore, adiponectin might also affect the development and progression of diabetic complications[4]. Generally, increased serum adiponectin concentrations are associated with a lower risk of type 2 diabetes, and Saraheimo *et al.*[5] reported that increased serum adiponectin is a diagnostic marker for the progression from macroalbuminuria to ESRD in type 1 diabetic patients. Furthermore, recent reports show that urinary adiponectin excretion might predict progression of kidney disease in diabetic patients[6]. Although this relationship has not been fully elucidated, urinary and serum adiponectin could play an important role in vascular and glomerular homeostasis through their anti-inflammatory and anti-atherogenic actions. Adiponectin decreased the degree of albuminuria in early-stage DN through the downregulation of transforming growth factor-beta, which induced cellular hypertrophy, increased collagen synthesis and upregulation of nephrin messenger ribonucleic acid expression, which sustains the size of the selective barrier of the kidney[7].

In a recent issue of *Diabetes Care,* Panduru *et al.*[8] reported a longitudinal association between urinary adiponectin and the progression of DN. This association was shown during a median follow up of 5.8 years in patients with type 1 diabetes from the Finnish Diabetic Nephropathy study, using Cox regression models and the Fine–Gray competing-risks regression model. Urinary adiponectin was a significant predictor of DN progression at any stage after adjusting for sex, total cholesterol, smoking status, glycosylated hemoglobin levels, waist-to-hip ratio, triglyceride levels and eGFR. However, after adjusting for AER, urinary adiponectin predicted only progression to ESRD in patients with macroalbuminuria at baseline. Additionally, in patients with macroalbuminuria, urinary adiponectin predicted progression to ESRD independently of serum adiponectin, and the tubular markers liver-type fatty acid-binding protein and kidney injury molecule-1. Combining urinary adiponectin levels and AER or eGFR could improve

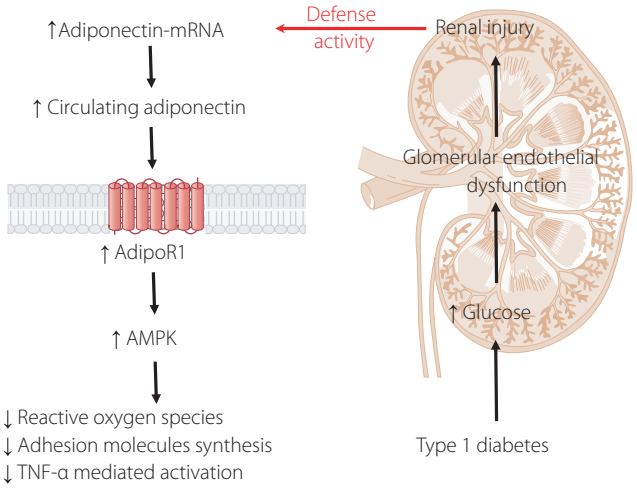

Figure 1 | The complex role of adiponectin in diabetic nephropathy. AdipoR1, adiponectin receptor 1; AMPK, adenosine monophosphate-activated protein kinase; mRNA, messenger ribonucleic acid; TNF-α, tumor necrosis factor-alpha.

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risk prediction for DN progression to ESRD. Evaluation of the added predictive ability of urinary adiponectin was carried out by various methods, including the following: increment of the area under the receiver operating characteristic curve, continuous net reclassification improvement, integrated discrimination improvement, increment of R^2 of the Cox models and mean risk difference between models.

Previous studies reported that urinary adiponectin levels were noticeably higher in patients with macroalbuminuria compared with patients with normoalbuminuria or microalbuminuria, and urinary adiponectin levels were correlated with serum adiponectin levels in patients with macroalbuminuria[6,9]. Furthermore, serum adiponectin levels were also elevated in type 1 diabetic patients with nephropathy[5]. The current study provides similar data, and suggests that hyperglycemia and microvascular damage in patients with DN could cause altered adiponectin function as part of a compensatory mechanism. Adiponectin increases adenosine monophosphate-activated protein kinase activity, and adenosine monophosphate-activated protein kinase has protective effects on endothelial cells through neutralization of reactive oxygen species, decrease of adhesion molecule synthesis and inhibition of tumor necrosis factor-alpha-mediated activation of nuclear factor kappa-light-chain-enhancer of activated B cells[7]. As such, adiponectin might play a protective role against renal disease, whereas stress on glomerular capillaries in diabetes accelerates adiponectin secretion from endothelial surfaces through proteolytic cleavage. As a result, increases in circulating adiponectin and enhanced filtration of circulating adiponectin could lead to increases in levels of urinary adiponectin (Figure 1)[10]. For this reason, urinary adiponectin, rather than serum adiponectin, reflected vascular and glomerular injury[11]. Additionally, the present study showed that AER, glycosylated hemoglobin, liver-type fatty acid-binding protein and kidney injury molecule-1 were associated with urinary adiponectin; these results suggest that urinary adiponectin levels can aid in the identification of glomerular damage as a result of poor glycemic control, as well as longer diabetes duration. These data are consistent with previous studies showing the association of worsening renal function with diabetes duration and an increase in urinary adiponectin levels[6].

In conclusion, urinary adiponectin might play a role in the identification of diabetic patients at increased risk of nephropathy progression. Urinary adiponectin levels, in addition to AER or eGFR, could contribute to more accurate detection of DN at all stages for the prevention of ESRD and cardiovascular disease.

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DISCLOSURE

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