Editorial

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A new journey to predict the prognosis of diabetic kidney disease

Da Woon Kim[1], Sang Heon Song[1,2]

[1]*Department of Internal Medicine and Biomedical Research Institute, Pusan National University Hospital, Busan, Republic of Korea*
[2]*Department of Internal Medicine, Pusan National University School of Medicine, Yangsan, Republic of Korea*

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Diabetic kidney disease (DKD), characterized by a gradually decreasing glomerular filtration rate (GFR) with or without albuminuria, has been considered the leading cause of chronic kidney disease (CKD) and end-stage kidney disease (ESKD) worldwide [1]. In patients with type 1 diabetes mellitus (DM) and type 2 DM (T2DM), the prevalence of DKD is 30% and 40%, respectively [2]. Because DKD is highly prevalent in patients with DM, it increases the risk of CKD progression along with cardiovascular morbidity and mortality, making early detection and prediction of the prognosis for DKD important [1].

Despite unneglectable limitations, the most commonly used prognostic factors of DKD are estimated GFR (eGFR) and albuminuria [1]. As DKD progresses, the number of nephrons decreases, and the single-nephron GFRs of the remaining nephrons increase by compensatory mechanisms. These changes increase glomerular hydraulic pressure and lead to glomerular hyperfiltration [3]. Therefore, similar eGFR levels can be observed in patients without functional nephron loss and in those with functional nephron loss and compensation, although these patients may have different prognoses. As for albuminuria, patients with DM can progress to ESKD without albuminuria (nonalbuminuric phenotype) [4], which suggests the limitation of albuminuria as a prognostic factor for DKD. Based on these findings, novel prognostic markers for DKD are necessary for appropriate patients' care in addition to these traditional factors in the clinical field.

Recently, omics-based assays have been widely used to investigate clinical biomarkers of kidney diseases, including DKD. However, only a few studies have examined the prognosis of patients with DKD. A recent proteomics study showed that the urinary proteome can predict the rapid deterioration of kidney function in DKD rather than albuminuria, a traditional prognostic marker [5]. In the field of metabolomics, Kwon et al. [6] suggest urinary myoinositol as a novel prognostic biomarker for DKD in this issue of *Kidney Research and Clinical Practice*. Metabolomics detects metabolites, regarded as the final downstream integration of gene, transcript, and protein functions, and has been used to identify potential biomarkers for the early detection and prediction of DKD progression. Niewczas et al. [7] identified specific uremic solutes and essential amino acids as contributors to the progression of ESKD in patients with T2DM. In this nested case-control study, 40 patients who progressed to ESKD during 8 to 12 years of follow-up and

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Correspondence: Sang Heon Song
Department of Internal Medicine, Pusan National University Hospital, Pusan National University School of Medicine, 179 Gudeok-ro, Seo-gu, Busan 49241, Republic of Korea. E-mail: shsong0209@gmail.com
ORCID: https://orcid.org/0000-0002-8218-6974

40 patients who did not were matched for baseline clinical characteristics, although the progressors had slightly lower eGFR and higher urinary albumin excretion. Some baseline uremic solutes and essential amino acids in the plasma are associated with an increased risk of progression to ESKD. Among the polyol-derived uremic solutes, plasma myoinositol was the most strongly associated metabolite, with an odds ratio of 3.2 (95% confidence interval, 1.7–5.9) after adjustment for the clinical covariates, eGFR, urinary albumin-to-creatinine ratio (uACR), and hemoglobin A1c (HbA1c). This finding suggests that plasma myoinositol is a potentially independent biomarker for predicting the progression to ESKD in patients with DKD.

Kwan et al. [8] evaluated the prognostic effect of 13 urine metabolites that were reduced in patients with DKD compared with healthy controls. A total of 1,001 patients from the Chronic Renal Insufficiency Cohort with DM were prospectively followed up for a median of 8 years, and among them, 359 (35.9%) progressed to ESKD. Clinical variables (race, mean arterial pressure, and urinary albumin level) were associated with eGFR decline and progression to ESKD. After adjusting for clinical variables, 3-hydroxyisobutyrate (3-HIBA), 3-methylcrotonylglycine, citric acid, and aconitic acid levels were associated with the slope. 3-HIBA and aconitic acid are associated with higher and lower risks of progression to ESKD, respectively.

A metabolomic study was also conducted in patients with nonproteinuric T2DM to investigate urinary metabolites predictive of low eGFR. All subjects had normoalbuminuria on at least two of the last three urinalyses. Urine metabolites of 40 patients with low eGFR (<60 mL/min/1.73 m^2) and 40 controls (eGFR, ≥60 mL/min/1.73 m^2) were analyzed. Eleven gas chromatography-mass spectrometry metabolites and 19 liquid chromatography-mass spectrometry metabolites were strongly associated with a low eGFR after correction for multiple hypothesis testing. However, the clinical factors associated with DKD progression were not adjusted in this study, and there is a limitation in that these metabolites have an independent prognostic effect on DKD progression [9].

A recent study investigated the potential prognostic biomarkers of DKD progression using the deep learning method of nontargeted metabolomics. A total of 135 patients with DKD grade 3 were classified as rapid decliners (whose annual eGFR change rate was below –10% of the baseline eGFR) and nonrapid decliners. Fourteen (10.4%) patients were classified as rapid decliners. Compared to nonrapid decliners, rapid decliners had lower eGFR and higher uACR. Metabolomic analyses were performed using plasma and urine samples from the patients. Only one metabolite, urinary 1-methylpyridine-1-ium (NMP), had a prognostic effect on DKD progression. By applying a deep learning method to identify potential biomarkers and physiological parameters predicting the prognosis of DKD, six identified metabolites and three unidentified metabolites, including urinary NMP, systolic blood pressure, and uACR, were shown to be predictive of DKD progression [10].

Along with previously reported metabolomic studies, Kwon et al. [6] investigated a prognostic biomarker predicting DKD and identified urine myoinositol as a novel biomarker. This study included 208 patients with stages 1 to 5 DKD and 26 healthy controls. A total of 103 patients (44.0%) progressed to ESKD, and 65 (27.8%) died during the median follow-up period of 4.5 years. While this study has the disadvantage of not being able to determine whether diabetes-induced kidney disease was the exact cause of kidney disease, it has the advantage of being a study of prognostic predictors in patients with ESKD. Metabolomics was performed using urine samples. Metabolomes involved in the urinary carbohydrate and tricarboxylic acid cycles were associated with an increased risk of progression to ESKD, death, and composite outcomes after adjusting for baseline clinical factors (age, sex, eGFR, urine protein-to-creatinine ratio [uPCR], HbA1c, and other laboratory findings). The net reclassification improvement (NRI) and integrated discrimination improvement (IDI) were used to assess the additive effect of urinary metabolites on serum creatinine and uPCR for the prediction of progression to ESKD; only myoinositol improved the predictive power (NRI, 2.9%, $p = 0.03$; IDI, 35.1%, $p = 0.02$). Since metabolomics itself has various confounders, including interindividual variability, diet, medication, the microbiome, and decreased kidney function, this study might also have some confounders that make the interpretation of the results difficult. However, with a previous study reporting plasma myoinositol as a potentially independent biomarker for predicting progression to ESKD [7], this study is meaningful in that it suggests that urine myoinositol is also a prognostic biomarker for DKD [6].

Although there have been great advances in metabolom-

ics investigating novel DKD biomarkers, further steps will be required. As most previous studies were cross-sectional, more prospective studies with larger numbers of patients are needed. Appropriate adjustments for aforementioned confounders in metabolomics are required to properly interpret the results of this study. Not only the investigation of novel biomarkers but also the validation of the discovered biomarkers in other cohorts is important to upgrade these metabolites to clinically meaningful tools for DKD management and improvement of patient outcomes.

Conflicts of interest

All authors have no conflicts of interest to declare.

Data sharing statement

The data presented in this study are available on request from the corresponding author.

ORCID

Da Woon Kim, https://orcid.org/0000-0002-9471-5976
Sang Heon Song, https://orcid.org/0000-0002-8218-6974

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