# Urine Proteomics Identifies Biomarkers for Diabetic Kidney Disease.

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## Abstract

**Chronic kidney disease (CKD) and end-stage renal disease (ESRD) are most commonly caused by type 2 diabetic kidney disease (ESRD). Although kidney biopsy is the "gold standard" for diagnosing diabetic kidney disease (DKD), it is an intrusive process that can be influenced by sample bias and personal judgement. It would be ideal to develop a non-invasive method to supplement kidney biopsy in the diagnosis and monitoring of DKD progression. We investigated the urine proteomes by liquid chromatography coupled with tandem mass spectrometry (LC–MS/MS) in this cross-sectional investigation, which included uncomplicated diabetes, without diabetes, and follow-up diabetic samples. To discriminate between simple diabetes, DKD, and other CKDs, we created logistic regression models. These findings were confirmed in a separate dataset. Finally, a four-protein classifier identified potential pre-DKD3 patients with DKD3 proteomic markers but no clinical diagnosis. Two putative pre-DKD patients have progressed to DKD3, according to follow-up research on 11 patients. Our findings show that urine proteomics has the potential to be a noninvasive technique for diagnosing DKD and selecting high-risk patients for progression monitoring.**

**Keywords**: Urine proteomics, biomarkers, diabetic kidney, disease, DKD3.

## Introduction

Diabetes affects more than 463 million people globally, accounting for about a quarter of the adult population. DKD, which is still a primary cause of morbidity and mortality in persons with type 2 diabetes, will develop in some of these people. Patients with DKD are at a high risk of developing ESRD and cardiovascular disease. As a result, disease management relies heavily on early detection, prevention, and treatment. DKD is diagnosed clinically based on eGFR, albuminuria, and the urine microalbumin creatinine ratio (UACR), as well as other clinical characteristics. Kidney biopsy is the "gold standard" for a definitive diagnosis of DKD, with an expert renal pathologist making the diagnosis from histological tissue. However, the technique is intrusive and sometimes risky, and human judgement might skew the evaluation process. Finding a noninvasive diagnostic that can complement or replace renal puncture is critical. According to clinical recommendations, DKD is split into five stages. The preclinical phases of DKDs, stage 1 (DKD1) and stage 2 (DKD2), are marked by an increase in glomerular filtration rate (GFR), normal albuminuria, or intermittent microalbuminuria. The development of clinical stage DKD3 is marked by persistent microalbuminuria, mild hypertension, and a normal or small reduction in GFR. Edema and hypertension are common clinical symptoms of DKD4, as is an increase in albuminuria, which is difficult to cure. As the glomerular filtration rate (GFR) decreases, the albumin-to-creatinine ratio (ACR) rises (> 300 mg/g) in overt DKD4. Taking any medicine could exacerbate the condition in this situation by increasing the stress on the kidneys. DKD progression can often be slowed or even stopped before it reaches stage 4 with adequate clinical intervention. As a result, monitoring DKD3 patients' renal function is crucial to medical treatment and delaying disease progression.

Several noninvasive methods for the examination of urine or serum biomarkers have been presented in recent years, most of which are based on 'omics' methodologies. Urinary proteome analysis is one of these methods that has gained traction and has the potential to be translated into clinical practise. Measuring the urinary proteome is non-invasive, and quantitatively measuring urinary proteins and peptides can be a useful tool for identifying disease stages and monitoring therapy response. Many efforts have been made to develop biomarkers for CKD that might be used to help DKD patients quantify their risk. A panel of biomarkers was identified from urinary peptides using high-resolution capillary electrophoresis combined with electrospray-ionization mass spectrometry, and they were reported to be able to distinguish healthy individuals from diabetic patients with persistent normal albuminuria, low-grade albuminuria, or nephropathy. It may also be able to identify patients with DKD from those with other CKDs. The particular protein identities of these peptide biomarkers, however, were unknown.

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## Conclusion

We used a urine proteomic workflow to undertake a cross-sectional assessment of patients with simple diabetes, DKD, and CKD in this study. We discovered biomarkers that could tell the difference between DKD and simple diabetes, as well as stage 4 DKD and stage 3 DKD. The categorization was validated in an independent dataset after the discovery dataset was used to build logistic regression models. According to bioinformatics, (upregulation of DKD4) complement cascade is a sign of DKD development. Furthermore, an algorithm was developed to identify DKD patients at an earlier stage. Patients with presumptive pre-DKD have advanced to DKD3 according to follow-up investigations. The potential of urine proteomics as a noninvasive technique for diagnosing DKD and identifying high-risk individuals for progression monitoring was proven in this study. During illness progression, the pathways discovered from variably secreted proteins gave vital data on biological foundation.

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