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# Beyond the Glomerulus—Kidney Tubule Markers and Diabetic Kidney Disease Progression



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Diabetic kidney disease (DKD) is a leading cause of chronic kidney disease (CKD) and end-stage kidney disease. Enthusiasm in the field of DKD therapy over the last 5 years has been fueled by the evolution of sodium-glucose co-transporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists. These medications have been shown to reduce kidney disease progression and risk of death in patients with diabetes with and without proteinuria. As we continue to expand the boundaries of who can receive these medications; from those with diabetes and proteinuria, to possibly all patients with CKD and heart failure, it is but natural to ask the question, "Who is likely to benefit from risk stratification and early intervention?"

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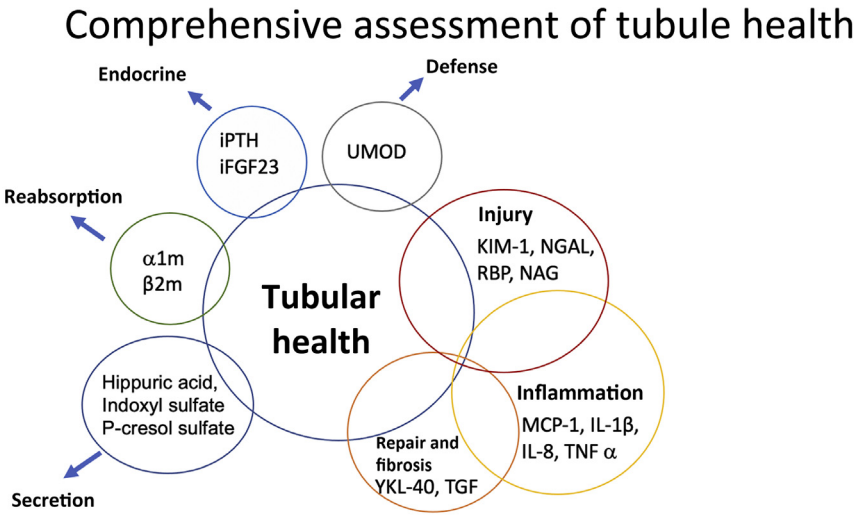
Although the most common markers for diagnosis and prognostication of DKD are albuminuria and estimated glomerular filtration rate (eGFR), their ability to predict progressive kidney function decline among individuals with type 2 diabetes mellitus (T2DM) has been shown to be modest,[1] especially given that overt proteinuria does not always herald progressive DKD in this population. Therefore, there have been increasing efforts focused on markers of kidney tubule function, injury, inflammation, and repair, to see if these can detect persons at risk for DKD.

The kidney tubule cells carry out numerous critical functions, including electrolyte transport, acid–base homeostasis, metabolite secretion, and endocrine functions, with the vast majority of energy expenditure within the kidney devoted to these tubular functions. Abnormalities in these key functions have been previously associated with CKD progression. Recently, urinary markers of proximal tubular damage have been associated with CKD progression among participants without diabetes,[2] but there remains a paucity of data on their role in persons at risk for DKD, and there is therefore a need for evaluating biomarkers including inflammation, injury, and tubulointerstitial fibrosis that encompass the complicated pathophysiology of DKD.

In this issue, Phanish *et al.*[3] investigated the role of urinary biomarkers of proximal tubule injury, inflammation, and fibrosis in CKD detection and progression among participants with DKD with and without albuminuria. They performed a single-center prospective cohort study among 388 persons with diabetes, of whom nearly 85% had type 2 diabetes mellitus (T2DM), and 10 healthy volunteers in the United Kingdom. Participants were required to have at least 3 eGFR measurements over a follow-up period of 5 years. At baseline, the investigators measured markers of glomerular damage (albumin), proximal tubular injury (retinol binding protein and *N*-acetyl-β-glucosaminidase (NAG), inflammation (monocyte chemotactic protein-1 [MCP1], interleukin 1β [IL 1β], interleukin 6 [IL 6], and tumor necrosis α [TNF-α]), and fibrosis (transforming growth factor β 1,2,3 [TGF β1, 2, 3]). Approximately half of the participants had albuminuria (albumin/creatinine ratio >3 mg/mmol). The investigators used 3 definitions for disease progression: (i) progression to CKD stage 3 or more; (ii) change in CKD stage; and (iii) a 30% or more decline in eGFR.

In the overall cohort, albumin-to-creatinine ratio, retinol-binding protein (RBP), NAG and neutrophil gelatinase-associated lipocalin were associated with higher odds of prevalent CKD, whereas in




iPTH, intact parathyroid hormone; iFGF23, intact fibroblast growth factor 23; UMOD, uromodulin; KIM-1, kidney injury molecule-1; NGAL, neutrophil- gelatinase associated lipocalin; RBP, retinol binding protein; NAG, N-acetyl-β-glucosaminidase; MCP1, monocyte chemoattract protein-1; IL-1β, interleukin 1 beta; IL-8, interleukin 8; TNF α, tumor necrosis factor alpha; YKL-40, chitinase-3-like protein; TGF, transforming growth factor; α1m, alpha-1 macroglobulin; β2m, beta-2 microglobulin

**Figure 1.** Comprehensive kidney tubule health panel. The figure represents the different axes of tubular function in addition to potential markers identifying stages of injury, inflammation, repair, and fibrosis. Together, a comprehensive tubule health panel lends itself to understanding the complex pathophysiology underpinning kidney function and health, beyond current glomerular markers.

patients without albuminuria, only NAG was significantly associated with CKD. Although it was also the only biomarker elevated in persons with eGFR >90 ml/min per 1.73m$^2$ without albuminuria, suggesting that it may help identify persons with "preclinical" DKD, as suggested by prior data,[4] it was not associated with more advanced CKD or with incident kidney disease.

The most promising urinary markers, aside from albumin, were RBP and MCP1, which were both statistically significantly associated with incident CKD, change in CKD stage, and a 30% or greater decline in eGFR in the overall cohort. Inflammatory markers were not individually associated with CKD progression; but, when combined, MCP1, IL-6, and gelatinase-associated lipocalin were associated with a 20% higher risk of incident CKD 3 and beyond. Overall, no individual nor combination of biomarkers substantially added to prediction of kidney disease.

Monocyte chemotactic protein-1 is a specific chemokine secreted in response to an inflammatory stimuli that has been found to be biologically active in the urine of patients with several glomerular diseases, including DKD.[4] Similar to the results found among persons with CKD but without diabetes in the Systolic Blood Pressure Intervention Trial (SPRINT), in which MCP1 was associated with a higher risk of 50% eGFR decline[5] and marker of proximal tubular dysfunction (α-1 microglobulin [α1m]) leading to increased risk of future acute kidney injury,[6] this study seems to indicate the role of proximal tubular dysfunction in DKD. RBP is a low-molecular-weight protein synthesized by the liver and is the carrier protein of vitamin A. It is freely filtered at the glomerulus and undergoes active uptake by the proximal tubule, similar to urinary albumin. Thus, elevated urine RBP levels may serve as a marker of proximal tubular dysfunction, especially in the setting of a relatively preserved GFR.[7] However, whether it significantly adds to albuminuria or existing proximal tubular biomarkers such as α1m needs to be determined.

The results from the study by Phanish *et al.* are in line with findings from a secondary analysis of data from the Action to Control Cardiovascular Disease Trial,[8] in which MCP1 indexed to urine creatinine was strongly associated with incident kidney function decline in persons with T2DM, independent of albuminuria and eGFR. Neither MCP1 nor any combination of other urine biomarkers studied substantially added to the predictive value of more traditional risk factors such as eGFR, albuminuria, and urine creatinine in predicting kidney function decline after stratifying by albuminuria status, with c-statistics between 0.71 and 0.74, which are similar to those seen in the current study (0.71).

A number of models already exist to predict the development and progression of CKD in patients with and without diabetes. The largest study, which included data from more than 800,000 persons with diabetes from the CKD Prognosis Consortium, yielded a c-statistic of 0.80 for predicting loss of kidney function using routinely

measured clinical variables.[9] Therefore, novel biomarkers of kidney function and injury will have to perform significantly better to be integrated into clinical practice for predicting outcomes.

Despite the lack of improvement in prediction, there is a role for biomarkers in helping us understand pathology that may often not be visible without performing a kidney biopsy. It is unlikely that a single biomarker can accurately capture the complicated pathology associated with CKD development and progression. A snapshot of "global kidney function" using a panel of biomarkers including filtration, reabsorption, secretion, and synthetic function (hormonal production) akin to a liver function panel may provide a comprehensive understanding of the underlying pathophysiology (Figure 1). Furthermore, the use of novel biomarkers may help enrich trials by recruiting participants, as has been done already in trials of acute kidney injury. This could potentially lead to cost reduction and to better-targeted therapies. However, given the abundance of markers being studied, using summarizing statistical techniques such as factor analysis may allow for reduction multi-marker panels to summary scores of biomarkers to improve predictive capacity and to reduce redundancy.

One limitation of the study by Phanish *et al*. was the lack of repeated measurements that would allow to determine whether longitudinal changes in tubular biomarkers are associated with increased CKD risk. Of note, in the above-mentioned study by Nadkarni *et al*., urine MCP1 levels were found to be relatively unchanged after 24 months and were not associated with the development of kidney outcome.[8] In addition, the current study did not adjust for baseline eGFR and lacked a validation cohort.

Overall, there is a growing body of evidence demonstrating the importance of kidney tubule markers independent of the influence of glomerular markers. Athough not yet ready for prime time, there is hope that future studies of tubular function, injury, inflammation, and repair markers will improve our knowledge about the role of the kidney tubule in maintaining health and aiding in the detection and progression of CKD among persons with diabetes, both with and without albuminuria.

## DISCLOSURES

Both authors declare no competing interests.

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