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Estimating tubular damage for predicting progression of chronic kidney disease—what are the implications for clinical practice and public health?

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In the last decade, several new urinary biomarkers have been put forward as markers of renal tubular damage or dysfunction [1, 2], and some of them have shown promise as early identifiers of acute kidney injury, which is an important area of unmet clinical need [3]. The relevance of the tubular damage biomarkers in chronic kidney disease (CKD) is less clear and the identification of patients at the highest risk of rapid CKD progression has been a challenge in clinical practice. In many CKD patients, kidney function remains relatively stable for years, whereas for others, kidney function declines rapidly, ultimately leading to end-stage renal disease and cardiovascular complications.

Current risk equations for end-stage renal disease are mostly based on the established kidney disease markers estimated glomerular filtration rate (eGFR) and albuminuria, and tubular dysfunction appears to be a separate aspect of kidney pathology not fully reflected by these biomarkers. Indeed, it has been suggested that there exists a group of patients with isolated tubular damage but with normal eGFR and albuminuria, who may have a worse prognosis for adverse cardiovascular outcomes [4]. Several tubular damage biomarkers have been reported as risk markers for CKD progression in the last decades; however in general, previous results on whether these markers add clinically valuable information have been conflicting and inconsistent [5, 6]. None of the proposed tubular damage biomarker-based risk prediction algorithms has so far reached broad clinical application. With the projected future increase in CKD burden combined with the emerging data on several new drugs (e.g. sodium-glucose cotransporter 2 inhibitors) that may slow the progression of CKD, improved risk prediction incorporating aspects of tubular damage may prove to be even more important in the future.

The potential of epidermal growth factor (EGF) as a biomarker was recently discovered by an elegant transcriptome-driven approach in kidney biopsies [7]. EGF is expressed by healthy tubular epithelial cells, and lower urinary EGF (uEGF) levels have been shown to reflect detrimental morphological changes in the kidney, including increased interstitial fibrosis and tubular atrophy. In previous biomarker studies in patients with CKD and diabetes, EGF has shown some promise as a suitable urinary biomarker candidate for discriminating between patients with a rapid CKD progression and those with a slow progression [8]. EGF has also been suggested to play a role in immunoglobulin A nephropathy [9] and obstructive nephropathy [10].

In this issue of *Nephrology Dialysis Transplantation*, Jon Viljar Norvik *et al.* [11] analysed data from two prospective cohorts of middle-aged adults without CKD or diabetes. The cohorts differed with regards to uEGF assay, urine sampling, and the method used to measure or estimate GFR. In order to assess whether uEGF could be a biomarker for rapid renal function loss not captured by established renal risk markers, the authors implemented a number of statistical tests, subgroup analyses and sensitivity tests using different outcome definitions. Interestingly, a consistent association between lower uEGF excretion and a more rapid kidney function decline (>3 mL/min/1.73 m^2/year) was found in both cohorts after adjusting for age, sex, baseline GFR and albuminuria. Moreover, some support for improved risk prediction beyond established kidney disease risk factors was presented (albeit no strong support for clinical utility). However, several of the sensitivity analyses and subgroup analyses were not statistically significant (perhaps in part due to limited statistical power) and the authors did not correct the significance level according to the multiple testing performed (raising the likelihood of false positives among the statistically significant results presented). Thus, even though the study by Norvik *et al.* [11] is a valuable addition to the literature, additional studies are needed to assess

the clinical benefits of uEGF as a potential biomarker for rapid kidney function decline and incident CKD in otherwise healthy persons.

Importantly, before uEGF or any other new kidney disease biomarker for rapid renal function decline can be introduced on a broad scale in clinical practice, several requirements need to be met, such as:

(i) The statistically and clinically significant added value for risk prediction, prognosis or decision-making beyond established kidney measures needs to be established and replicated in independent settings.
(ii) Calibrated, economically viable and readily implementable biomarker assays need to be available, and clinically meaningful biomarker thresholds need to be defined in order to guide decision-making.
(iii) There is a need for randomized trials to prove that targeted interventions are beneficial in those persons identified as high risk by the new biomarker.
(iv) Thorough cost/benefit analyses for screening programmes with the new biomarker should be performed.

Whether urinary EGF can be useful in this context remains to be assessed in future studies.

On a more general note, despite the substantial public health impact of CKD, disease awareness remains low [12, 13] and few countries have explicit programmes aimed at preventing CKD and its consequences. However, there is a considerable gap between the current kidney disease screening guidelines and the diagnostic, staging and referral patterns of CKD in clinical practice, even in high-income countries [14]. Thus, to maximize the benefits to global kidney health, stronger adherence to guideline-recommended CKD screening using established kidney disease biomarkers would likely have a greater impact on public health at the present moment than introducing novel kidney biomarkers.

CONFLICT OF INTEREST STATEMENT

C.N. reports no conflicts of interest. J.Ä. has served on advisory boards for AstraZeneca and Boehringer Ingelheim, and has received lecturing fees from AstraZeneca and Novartis, all unrelated to the present editorial.

(See related article by Norvik *et al.* Urinary excretion of epidermal growth factor and rapid loss of kidney function. *Nephrol Dial Transplant* 2021; 36: 1882–1892)

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