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CLINICAL RESEARCH

Prediction of Chronic Kidney Disease Stage 3 by CKD273, a Urinary Proteomic Biomarker

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Introduction: CKD273 is a urinary biomarker, which in advanced chronic kidney disease predicts further deterioration. We investigated whether CKD273 can also predict a decline of estimated glomerular filtration rate (eGFR) to <60 ml/min per 1.73 m^2.

Methods: In analyses of 2087 individuals from 6 cohorts (46.4% women; 73.5% with diabetes; mean age, 46.1 years; eGFR ≥ 60 ml/min per 1.73 m^2, 100%; urinary albumin excretion rate [UAE] ≥20 μg/min, 6.2%), we accounted for cohort, sex, age, mean arterial pressure, diabetes, and eGFR at baseline and expressed associations per 1-SD increment in urinary biomarkers.

Results: Over 5 (median) follow-up visits, eGFR decreased more with higher baseline CKD273 than UAE (1.64 vs. 0.82 ml/min/m^2; $P < 0.0001$). Over 4.6 years (median), 390 participants experienced a first renal endpoint (eGFR decrease by ≥10 to <60 ml/min per 1.73 m^2), and 172 experienced an endpoint sustained over follow-up. The risk of a first and sustained renal endpoint increased with UAE (hazard ratio ≥ 1.23; $P \leq 0.043$) and CKD273 (≥ 1.20; $P \leq 0.031$). UAE (≥20 μg/min) and CKD273 (≥0.154) thresholds yielded sensitivities of 10% and 23% and specificities of 92% and 90% ($P \leq 0.0001$ for difference between UAE and CKD273 in proportion of correctly classified individuals). As continuous markers, CKD273 ($P = 0.039$), but not UAE ($P = 0.065$), increased the integrated discrimination improvement, while both UAE and CKD273 improved the net reclassification index ($P \leq 0.0003$), except for UAE per threshold ($P = 0.086$).

Discussion: In conclusion, while accounting for baseline eGFR, albuminuria, and covariables, CKD273 adds to the prediction of stage 3 chronic kidney disease, at which point intervention remains an achievable therapeutic target.

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Chronic kidney disease (CKD), defined as abnormalities of kidney structure or function lasting for more than 3 months,[1] is a major health problem affecting 10% of the general population and thereby decreases the quality of life of millions of people.[2–4] Compared with other chronic age-related illnesses, relatively few clinical trials have addressed the prevention of progression in patients with CKD.[5] One of the underlying reasons is the long follow-up required to reach severe endpoints, such as doubling of serum creatinine[6] or a 50% decrease in the estimated glomerular filtration rate (eGFR),[7] the need for renal replacement therapy,[6,7] or death.[6] In 2016, the European Medicines Agency (EMA) proposed that primary efficacy endpoints in trials with renal outcomes can be the prevention or delay of renal function decline defined as time to or the incidence rate of stage 3 CKD with or without albuminuria or proteinuria.[8] A recent meta-analysis of 1.7 million subjects demonstrated that a 30% reduction in eGFR over 2 years was a predictor of end-stage renal disease and death[9] and thereby supports the concept of using shorter-term endpoints as proposed by the EMA.

Capillary electrophoresis coupled with high-resolution mass spectrometry (CE-MS) enables detection of more than 5000 peptide fragments in urine samples.[10–12] CKD273 is a multidimensional urinary biomarker consisting of 273 peptide fragments,[10,13] which in patients with advanced CKD predicts further deterioration of renal function.[14,15] The Food and Drug Administration recently encouraged further studies of CKD273 as a tool for the diagnosis and risk prediction in CKD.[13] In keeping with the EMA recommendation[8] and the Food and Drug Administration statement,[13] the objective of the present study was to investigate whether CKD273 also predicts the incidence of eGFR to less than 60 ml/min per 1.73 m^2, at which point intervention[16] is still an option before structural alterations associated with later stages of CKD render stopping or reversing the disease processes difficult, if not impossible.

METHODS

Participants

The Human Urine Proteome Database available at Mosaiques Diagnostics (Hannover, Germany)[17] includes anonymized clinical information on participants enrolled in several studies, as well as urinary proteomic signatures, including CKD273. These studies comply with the Declaration of Helsinki[18] and received ethical approval from the pertinent institutional review board. Q3 All participants gave informed written consent. The Ethics Committee of the University of Glasgow authorized the current analysis (approval number 3115-2016). To be eligible for analysis, the following criteria had to be fulfilled: (i) eGFR at baseline of 60 ml/min per 1.73 m^2 or higher; (ii) repeat assessment of eGFR during a follow-up of at least 2 years; and (iii) information available on clinically relevant covariables, including sex, age, systolic and diastolic blood pressure, serum creatinine, and albuminuria.

The number of participants in the Human Urine Proteome Database complying with the aforementioned eligibility criteria totaled 2087. Participants were: (i) patients enrolled in the Diabetes Retinopathy Candesartan Trials with type 1 (DIRECT1; $n = 740$)[19] and type 2 (DIRECT2; $n = 618$)[20] diabetes; (ii) patients with type 2 diabetes recruited into a Dutch study (PREDICTIONS)[21] aimed at identifying disease pathway–specific biomarkers ($n = 96$), (iii) and patients with diabetes recruited from clinics in Australia ($n = 47$)[22] and Hannover, Germany ($n = 22$).[16] The remaining 564 analyzed individuals were enrolled in the Flemish Study on Environment, Genes and Health Outcomes (FLEMENGHO).[23]

Assessment of Renal Function

Estimated GFR was calculated from serum creatinine by the Chronic Kidney Disease Epidemiology Collaboration equation.[24] The primary renal endpoint was a decrease in eGFR from baseline to follow-up by at least 10 ml/min per 1.73 m^2 to less than 60 ml/min per 1.73 m^2. A sustained renal endpoint required that the impairment of glomerular function be maintained for at least 3 months with no increase above 60 ml/min per 1.73 m^2 at any time during further follow-up. Estimated GFR categories, defined according to the National Kidney Foundation Kidney Disease Outcomes Quality Initiative guidelines,[25] were eGFR ≥90, 89–60, 59–45, 44–30, 29–15, and <15 ml/min per 1.73 m^2 for stages 1, 2, 3A, 3B, 4, and 5, respectively. In keeping with the suggestion to use declines in eGFR smaller than those associated with a doubling of serum creatinine,[9] in a sensitivity analysis, we redefined the renal endpoint as a decrease in eGFR by 30% or more over 2 years.

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