Dickkopf-3 (DKK3) in Urine Identifies Patients with Short-term Risk of eGFR Loss

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Introduction

Accurate assessment of short-term eGFR decline in CKD patients is challenging, but mandatory. We explored the clinical utility of urinary Dickkopf-3 (DKK3), a stress-induced tubular epithelia-derived pro-fibrotic glycoprotein as a biomarker of short-term eGFR loss, i.e. within the next 12 months.

Methods

We prospectively assessed estimated glomerular filtration rate (eGFR) and urinary DKK3 levels in patients with CKD of various etiologies (N=775), and annual follow-ups (N=2,035 patient years). Urinary DKK3 was also measured in a general population sample (N=481). In patients with diagnostic kidney biopsies (N=119), and in patients with IgA nephropathy, under treatment (randomized STOP-IgAN trial, N=96).

Results

Median urinary DKK3/creatinine concentration was significantly higher in CKD patients as compared to controls (431 [IQR 1,388] vs. 33 [IQR 126] pg/mg). In the prospective CKD cohort, urinary DKK3/creatinine >4,000 pg/mg was independently associated with a mean annual decline in eGFR of 7.6% (95% CI: -10.9 to -4.2%; p<0.001) after multiple adjustments. Urinary DKK3 significantly improved prediction of kidney function loss as compared to eGFR or albuminuria alone. In kidney biopsies, urinary DKK3/creatinine levels were related to the extent of tubulointerstitial fibrosis. In STOP-IgAN patients, a rise in urinary DKK3 was associated with a significant (p<0.001) eGFR decline within 6 months, whereas stable/decreasing urinary DKK3 indicated a more favorable course of eGFR. This finding was independent of randomization to the intervention arms.

Conclusion

Urinary DKK3 identifies patients at high risk for eGFR loss within the next 12 months and represents a novel diagnostic tool for personalized treatment in these patients.

Urinary DKK3 identifies patients with short-term risk of eGFR loss

Overview of studies and cohorts.

(A) CARE FOR HOME study (Observational study of CKD patients with various CKD etiologies)

(B) STOP-IgAN study (Randomized controlled study of patients with IgA nephropathy)

(C) Cross sectional cohorts

Acute or chronic diseases (N=189)

Supportive care plus immunosuppressive treatment (N=28)

Supportive care (N=57)

I LIKE HOMe study
Kidney biopsy study, N=76
(Observational study of CKD patients with various CKD etiologies)

CARE FOR HOMe study
Kidney biopsy study, N=127 (total=2,035 patient years)

Supportive care plus immunosuppressive treatment, N=28

Supportive care, N=57

Prevalence of tubulointerstitial fibrosis in patients with CKD

Distribution of urinary DKK3/creatinine levels (on a logarithmic scale) in the participants of the I LIKE HOME cohort representing the general population (N=481) compared to CKD patients from the CARE FOR HOME cohort (N=119) with no relevant overlap between subject from the general population and CKD patients. Urinary DKK3/creatinine levels were correlated in a linear regression analysis to the extent of tubulointerstitial fibrosis and to patients with CKD of other etiology (N=186).

Urinary DKK3 predicts short-term risk of eGFR loss

(A) Restricted cubic spline plots of the association between change of estimated glomerular filtration rate (eGFR) and urinary DKK3/creatinine concentrations in the CARE FOR HOME study. The red line indicates the estimated change of eGFR with the addition of urinary DKK3/creatinine. Each vertical line indicates DKK3/creatinine levels used as cut-off in subgroups analyses. Blue circles show the association between urinary DKK3/creatinine concentrations. All plots are adjusted for age, gender, body mass index, systolic blood pressure, diabetes, smoking status, eGFR and log albuminuria.

(B) Restricted cubic spline plots of the association between change of estimated glomerular filtration rate (eGFR) and urinary DKK3/creatinine concentrations in the I LIKE HOME study. The red line indicates the estimated change of eGFR with the addition of urinary DKK3/creatinine. Each vertical line indicates DKK3/creatinine levels used as cut-off in subgroups analyses. Blue circles show the association between urinary DKK3/creatinine concentrations. All plots are adjusted for age, gender, body mass index, systolic blood pressure, smoking status, eGFR and log albuminuria.

Urinary DKK3 predicts changes of eGFR in patients with IgA nephropathy (STOP-IgAN trial)

(A) Restricted cubic spline plots of the association between change of estimated glomerular filtration rate (eGFR) and urinary DKK3/creatinine concentrations in the STOP-IgAN trial adjusted for age, gender, body mass index, systolic blood pressure, smoking status, eGFR and log albuminuria.

(B) Restricted cubic spline plots of the association between change of eGFR (%) and change of urinary DKK3/creatinine during early treatment (Run-In Phase) and late treatment (Treatment Phase) in participants of the STOP-IgAN trial adjusted for age, gender, body mass index, systolic blood pressure, smoking status, eGFR and log albuminuria.

Urinary DKK3 is a tubular stress sensor

(a) Tubulointerstitial fibrosis in patients with end-stage renal disease according to urinary DKK3/creatinine concentrations.

(b) Representative kidney biopsy specimens from 3 patients with membranous nephropathy paper red and 5 patients with focal segmental glomerular sclerosis paper red according to urinary DKK3/creatinine concentrations.

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