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Dickkopf 3 As A Novel Biomarker of The Kidney Injury

Amr Mohamed Sameh Ibrahim , Adel AbdElmohsen Ghorab, Medhat Ibrahim Mahmoud, Ahmed Mohamed Salah Ibrahim

Internal Medicine Department, Faculty of Medicine, Zagazig University, Egypt

Amrlabban7@gmail.com

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Abstract: Chronic kidney disease (CKD) represents a global public health problem and is associated with substantial morbidity, reduced life expectancy and high healthcare resource utilization. Around 800 million people or as many as 15% of the population worldwide are affected by CKD, and the proportion of CKD patients in the total population increases significantly with age. Dickkopf-3 (DKK3) belongs to a family of glycoproteins (DKK1–4) that modulate the Wnt signalling pathway. They are encoded by DKK genes, which comprise an evolutionary conserved small gene family of four members (Dkk1–4) and the Dkk3-related gene, Dkkl1 (soggy). DKK proteins play an important role in vertebrate development, where they locally inhibit Wnt-regulated processes such as limb development and eye formation. Besides, several studies have shown significant effects of DKK proteins on Wnt/β-catenin signalling in experimental CKD models. In a study using high-throughput single-nucleotide polymorphism (SNP) genotyping of 173 candidate genes in 794 white patients from 227 families with autosomal dominant polycystic kidney disease (ADPKD), a genetic variation within the DKK3 locus was associated with more severe disease progression. It has been shown that urinary concentrations of DKK3 significantly increase in mice fed with an adenine-rich diet, whereas DKK3 was not detectable in the urine of healthy mice. To determine the DKK3-producing renal cell type, reporter mice have been generated expressing luciferase and mCherry under the regulatory sequences of the Dkk3 gene.

Keywords: Dickkopf 3, Kidney Injury

Introduction:

Chronic kidney disease (CKD) represents a global public health problem and is associated with substantial morbidity, reduced life expectancy and high healthcare resource utilization. Around 800 million people or as many as 15% of the population worldwide are affected by CKD, and the proportion of CKD patients in the total population increases significantly with age **(1)**

The major causes of progressive CKD in the Western world are diabetic and/or hypertensive kidney injury, but also (repetitive) acute kidney injury (AKI) is nowadays recognized as an

emerging cause of progressive CKD and terminal kidney failure as well. CKD progression is defined by a decrease in kidney function until end-stage kidney disease (ESKD) is reached, necessitating renal replacement therapy **(2)**.

Starting in the earliest stages, CKD is accompanied by a variety of co-morbidities and non-renal complications contribute to the particular high, e.g. cardiovascular mortality in patients with CKD. In this respect, progressive CKD leading to severe uraemic complications can be seen as a 'systemic' disease with a critical impact on virtually all organ systems. Thus, reliable identification of patients with ongoing CKD progression has broad consequences not only for their well-being but also for saving of healthcare resources **(1)**

Currently, established markers for prediction of long-term CKD progression are the glomerular filtration rate (GFR) and albuminuria. In the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines, patients with CKD of diffserent aetiologies are categorized as having low, moderate, high or very high risk for kidney disease progression according to their estimated GFR (eGFR) and albuminuria **(3)**.

However, the individual course of CKD is difficult to predict even within a specific risk category, particularly under disease-modifying therapeutic interventions. Hence, kidney failure risk equations have been developed in order to optimize the prediction of CKD progression. These are widely based on eGFR and albuminuria, but also include other clinical and biochemical variables **(4)**.

While further refining of these equations with inclusion of more progression indicators can improve their accuracy at large population level to predict the 2- or 5-year probability for ESKD (i.e. dialysis or transplantation), the individual CKD course remains variable and difficult to predict by general equations. Indeed, studies have shown that patterns of CKD progression include linear and non-linear GFR trajectories. Moreover, kidney function can also remain stable for years in some individuals without any progression of their kidney disease. For example, in 1.7 million participants from 35 cohorts with 12 344 ESKD events, a highly variable individual CKD progression was observed even within subjects classified in the same KDIGO risk category **(1)**

In patients with a baseline eGFR of 35 mL/min/1.73 m2, in whom eGFR remained stable within the first 2 years of the subsequent observation period, the risk of reaching ESKD after 10 years was 18%. In contrast, patients with the same baseline eGFR (i.e. 35 mL/min/1.73 m2) who experienced a mean eGFR decline of 57% within the first 2 years had a risk of 99% to reach ESKD in the following 10 years **(5)**

Thus, identifying subjects at risk for faster progression—whatever the cause may be—is challenging, but of importance for the individual patient. Finally, results of studies in the general population and in patients at high risk for progressive CKD revealed that a substantial GFR loss may occur even in the absence of higher-grade albuminuria (termed non-proteinuric CKD pathway). Therefore, biomarkers that allow for identification of patients with CKD progression are needed **(6)**.

The WNT Pathway, Tubular Cell Stress And Progressive Tubulointerstitial Fibrosis

The renal tubulointerstitial compartment not only represents the major compartment of the kidney, but is also vulnerable to a variety of injuries such as hypoxia and toxicity-induced damage. While it has long been postulated that tubular epithelia cells (TECs) represent the main victim of such injury, an experimental data identified TECs as an important factor in CKD progression **(7)**.

In response to injury, TECs can undergo alterations in phenotype and function, and subsequently act as pro-inflammatory and pro-fibrotic cells. They produce various bioactive molecules that perpetuate the damage, eventually leading to epithelial–mesenchymal transition and irreversible renal scaring. The latter is referred to as tubulointerstitial fibrosis and represents the common pathological hallmark of a etiologically different CKD entities that finally results in organ failure **(8)**.

However, biomarkers for this specific renal pathologic course are not available so far. This is mandatory, since a better understanding of the mechanisms leading to tubulointerstitial fibrosis is necessary for the development of specific therapeutics to halt CKD progression. In experimental studies, many pro-fibrotic molecules secreted by TECs have been identified, e.g. transforming growth factor beta (TGF-β) and platelet-derived growth factor. Moreover, modulation of specific pathways such as Notch and the Wingless-Int1 (Wnt)/β-catenin pathway involved in tubulointerstitial fibrosis by TECs has been documented **(9)**.

The Wnt/β-catenin signalling cascade plays an important role in distinct cellular processes such as proliferation, migration, polarity and expression of pro-fibrogenic cytokines. Many factors are capable of activating or to inhibiting Wnt signalling. In addition to the activity and/or concentration of the ligands and co-activators/co-inhibitors, the time and duration of activity and the crosstalk with other cytokine-triggered pathways are important determinants of the Wnt signalling. In the kidney, the Wnt pathways represent a complex system, whose effects may differ in acute versus chronic TEC injury models **(10)**.

Depending on the level of activity and the duration of activation, either repair processes predominate or kidney damage progresses. It has been postulated that TECs can produce Wnt ligands, which then activate the neighbouring fibroblasts in a paracrine manner to promote tubulointerstitial fibrosis and thus progressive CKD **(11)**.

Dickkopf-3 In Kidney Disease

Dickkopf-3 (DKK3) belongs to a family of glycoproteins (DKK1–4) that modulate the Wnt signalling pathway. They are encoded by *DKK* genes, which comprise an evolutionary conserved small gene family of four members (*Dkk1–4*) and the Dkk3-related gene, *Dkkl1* (soggy). DKK proteins play an important role in vertebrate development, where they locally inhibit Wnt-regulated processes such as limb development and eye formation **(12)**.

Besides, several studies have shown significant effects of DKK proteins on Wnt/β-catenin signalling in experimental CKD models. In a study using high-throughput single-nucleotide polymorphism (SNP) genotyping of 173 candidate genes in 794 white patients from 227

families with autosomal dominant polycystic kidney disease (ADPKD), a genetic variation within the *DKK3* locus was associated with more severe disease progression **(13)**.

A study provided evidence that DKK3 is expressed in the developing kidney, suppressed in adult life and neo-expressed under pathological conditions, i.e. kidney tissue injury. In *Dkk3*-deficient mice, TEC damage and renal interstitial fibrosis were significantly reduced as compared with wildtype mice after unilateral ureter ligation as well as in an adenine nephropathy mouse model. Similar results were obtained after antibody-mediated blockade of DKK3. In parallel, the authors observed an accumulation of T lymphocytes (i.e. mainly Foxp3+ regulatory T cells and interferon γ-producing Th1 cells) within the kidneys of *Dkk3*−/− mice after unilateral ureter ligation **(1)**

However, the authors found that genetic deficiency of *Dkk3* within tubular epithelial cells by using *Dkk3*fl/fl*Pax8*Cre mice was sufficient to prevent kidney fibrosis and tubular injury after unilateral ureter ligation. This points to a pivotal role of TEC during kidney fibrosis. DKK3 seems to be a member of evolutionarily conserved gene clusters, which are active during developmental processes, silenced thereafter and re-expressed in disease ('stress') states. Therefore, it is of interest that previous *in vitro* experiments revealed that DKK3 can either stimulate or suppress canonical Wnt/β-catenin signalling, depending on the tissue studied **(14).**

Urinary Dkk3: Source and Origin

It has been shown that urinary concentrations of DKK3 significantly increase in mice fed with an adenine-rich diet, whereas DKK3 was not detectable in the urine of healthy mice. To determine the DKK3-producing renal cell type, reporter mice have been generated expressing luciferase and mCherry under the regulatory sequences of the *Dkk3* gene. In healthy control mice, no luciferase activity was detected using bioluminescence imaging. In contrast, 2 days after unilateral ureter ligation, luciferase activity has been detected within the injured kidney. mCherry fluorescence co-localized with aquaporin 1 (i.e. a marker for proximal TEC) and to a weaker extent with aquaporin 2 (i.e. a marker for distal TEC) and was not detectable in other compartments of the kidney **(15)**.

Thus, TEC appears to be the sole source of DKK3 within the kidney. Accordingly, it was found that urinary DKK3 concentrations were significantly higher in patients with CKD as compared with apparently healthy subjects from the general population. Since DKK3 is also expressed in other organs, measurable amounts of DKK3 are present in plasma. This raises the possibility that urinary DKK3 may also originate from filtered plasma DKK3 after glomerular injury. The predicted molecular weight of DKK3 is 38 kDa. However, it has been shown that DKK3 may be substantially glycosylated, which increases its molecular weight to 60–70 kDa **(1)**

It was found that the urinary concentrations of DKK3 only correlated with albuminuria in patients with CKD and not in subjects from the general population. The correlation coefficient for urinary DKK3 and albuminuria was 0.258, indicating that albuminuria accounts for 25.8% of the variability of urinary DKK3. In the CARE FOR HOME

(Cardiovascular and Renal Outcome in CKD2–4 Patients) trial, a study comprising 575 CKD patients of various aetiologies, higher albuminuria (>300 mg/g creatinine) was associated with higher urinary DKK3 levels as compared with subjects with urinary albumin excretion <30 mg/g. However, in 48.6% of the subjects with higher grade albuminuria, urinary DKK3 levels remained low (i.e. <1000 pg/mg creatinine) and in some patients even below the detection limit **(16)**.

Therefore, it remains unclear as to why plasma DKK3 may not cross the glomerular barrier in these patients although the molecular mass of plasma DKK3 may not significantly differ from, e.g. albumin. This may be caused by the interaction of plasma DKK3 with other circulating plasma components or the formation of high molecular weight complexes preventing them from crossing the glomerular barrier **(17)**.

Future studies are necessary to explore the detailed route of urinary and plasma DKK3 during kidney injury. In as yet unpublished studies, no significant correlation between DKK3 in plasma and urine was found. Nevertheless, since DKK3 is only expressed in TEC within the kidney after injury, urinary DKK3 may serve as a non-invasive diagnostic biomarker for ongoing TEC injury and progressive CKD. For the detection of DKK3 in human urine, antibodies against DKK3 produced by hybridoma cells were raised in the German Cancer Research Centre in Heidelberg, and an enzyme-linked immunosorbent assay (ELISA) was designed with the detection conditions specifically adjusted for recognition of the DKK3 protein in human urine **(16)**.

The ELISA is certified for diagnostic use in humans in the EU (ReFiNE, DiaRen UG, Homburg/Saar, Germany). Studies have documented that DKK3 is stable in cold-stored urine samples (at 4°C) for up to 24 h (~10% breakdown). Alternatively, urine samples (0.5 mL) can be immediately frozen at −20°C (for longer periods at −80°C) until they are measured. The lower detection limit of the assay is 30 pg/mL. The intra-assay test variabilities of repeated urine sample measurements are 3.1% in the lower (~500 pg/mL) and 3.5% in the higher (~1500 pg/mL) detection range. The values for interassay test variability are 4.7% in the lower and 5.1% in the higher detection range. There is no cross-reactivity with other proteins of the DKK family **(1)**

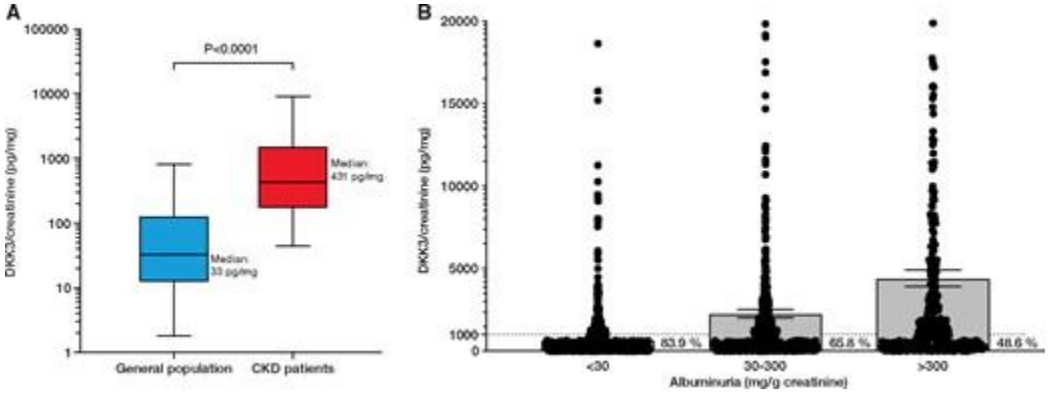

Figure 1: (A) Urinary DKK3 concentrations in subjects of the general population and patients with various CKD aetiologies. These include diabetic and/or hypertensive

kidney injury, glomerulonephritis, interstitial nephritis, ADPKD and others. (B) Urinary DKK3 concentrations in patients with CKD according to albuminuria. The percentage indicates the proportion of patients per group with urinary DKK3 concentration <1000 pg/mg creatinine (14).

Dkk3—A Biomarker of Short-Term Ckd Progression

Based on these findings, a group assessed the association between urinary DKK3 and tubulointerstitial fibrosis in a cohort of patients who underwent a diagnostic kidney biopsy at the University Hospital Innsbruck, Austria, and in kidney biopsy specimens of Supportive Versus Immunosuppressive Therapy for the Treatment of Progressive IgA Nephropathy (STOP-IgAN) trial participants before study inclusion. Interestingly, there was elevated urinary DKK3 concentrations to be significantly associated ($P < 0.001$) with higher-grade tubulointerstitial fibrosis in the biopsy specimens of both, patients with primarily glomerular diseases as well as in patients with primarily interstitial diseases **(16)**.

In order to evaluate this issue further in humans, the relationship between urinary DKK3 concentrations and annual changes of eGFR was assessed in the prospective CARE FOR HOME study with a mean follow-up of 5.1 years, comprising patients of various CKD aetiologies. For this purpose, a total of 2035 person-years were available for a 1-year block analysis from annual patient visits **(1)**

Moreoever, urinary DKK3 levels in patients with IgA nephropathy was measured, who participated in the randomized STOP-IgAN trial. In the CARE FOR HOME study, urinary DKK3 concentrations were significantly and independently associated with an eGFR decline in the subsequent 12 months after adjustment for a variety of clinical parameters including baseline eGFR and albuminuria. These findings were confirmed in the STOP-IgAN trial, where urinary DKK3 >1000 pg/mg creatinine was independently associated with a mean eGFR decline of 12.2% during the 6-month run-in phase **(16)**.

In STOP-IgAN, adding urinary DKK3 to a model comprising age, sex, body mass index, systolic blood pressure, eGFR and albuminuria significantly increased integrated discrimination improvement, net reclassification improvement (NRI) and c-statistics for the prediction of >0 and >5% decrease of eGFR during the run-in phase. For instance, the area under the curve for the prediction of >5% decrease of eGFR significantly increased from 0.68 [95% confidence interval (95% CI) 0.57–0.80] to 0.81 (95% CI 0.71–0.91; $P = 0.005$) with an NRI of 0.29. Notably, in a previous publication of the STOP-IgAN study group, neither NGAL, KIM-1, calprotectin nor [TIMP2]*[IGFBP7] were associated with progression of IgA nephropathy or the response to immunosuppression **(16)**.

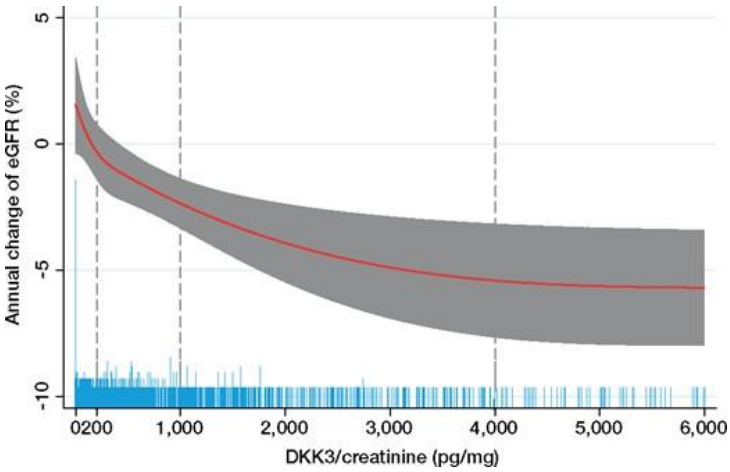

Figure 2: Association between urinary DKK3 and subsequent change of eGFR within the next 12 months in patients with various CKD aetiologies. Urinary DKK3 levels were normalized to urinary creatinine concentrations to account for dilution of the urine. All analyses were adjusted for age, gender, body mass index, systolic blood pressure, diabetes, smoking status, eGFR and log albuminuria **(1)**

Within the following first 6 months of the treatment phase, a rise in urinary DKK3 concentration was associated with a significant eGFR decline, whereas stable or decreasing urinary DKK3 indicated a more favourable course of kidney function. This result was independent of the randomization to the treatment arms. These findings highlight urinary DKK3 as a biomarker for short-term CKD progression, which may be of importance for nephrologists in particular for monitoring therapies that slow down or even prevent progression **(16)**.

The evaluation of short-term loss of GFR is a different approach from predicting long-term CKD prognosis by looking at predefined renal endpoints such as ESRD or 40% GFR decrease after several years. The latter gives a risk estimate of how many patients will reach a renal endpoint, while urinary DKK3 indicates short-term loss of kidney function in the individual patient. The association between urinary DKK3 and the aforementioned predefined renal endpoints has to be determined in future studies **(1)**

In both cohorts, the CARE FOR HOME study and the randomized STOP-IgAN trial, changes in urinary DKK3 levels were independently associated with changes in eGFR even after adjustment for albuminuria. Moreover, urinary DKK3 also predicted the decline in kidney function in patients with normal albumin excretion rate. This indicates that albuminuria/proteinuria and secretion of DKK3 in the urine may not be related to the same pathophysiological mechanisms. Further studies are thus warranted to explore the mechanisms of kidney disease progression in non-proteinuric CKD **(15)**.

To visualize the individual course of DKK3 in patients with primary kidney diseases (i.e. complement C3 glomerulonephritis, granulomatosis with polyangiitis and microscopic polyangiitis), urinary DKK3 concentrations was studied in these patients after specific treatment initiation. Notably, urinary DKK3 was found to decline within 30 days after

treatment initiation (either cyclophosphamide or rituximab/corticosteroids). Urinary DKK3 normalized earlier than kidney function improved. Larger studies have been recently initiated to determine whether DKK3 in urine might signify treatment success of distinct CKD entities even before kidney function (i.e. GFR) improves or stabilizes **(1)**

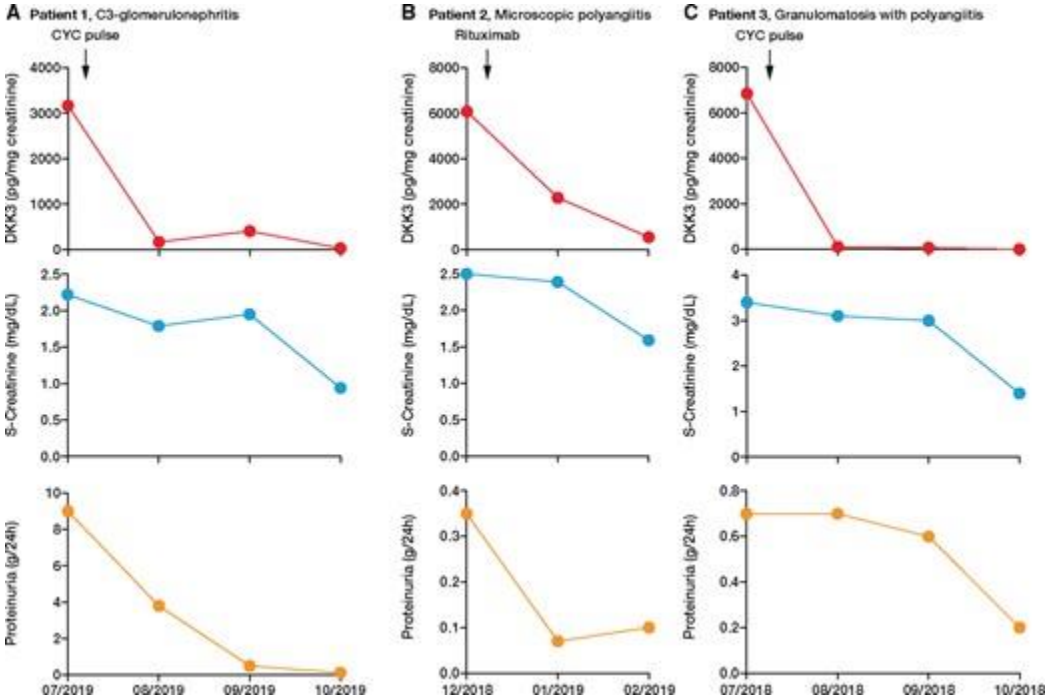

Figure 3: Individual course of urinary DKK3, serum creatinine and proteinuria in (A) a patient with biopsy-proven complement C3 glomerulonephritis, (B) a patient with biopsy-proven microscopic polyangiitis and (C) a patient with biopsy-proven granulomatosis with polyangiitis. Arrows indicate the initiation of specific therapies (CYC, cyclophosphamide or rituximab) **(1)**

Dkk3—A Biomarker for Risk Prediction Of Aki And Aki–Ckd Transition

It is well recognized that AKI—particularly repetitive—represents an emerging cause of progressive CKD and ESKD. For example, in patients undergoing cardiac surgery, AKI represents the most frequent complication, which occurs in 26.0–28.5% of the patients **(18)**. The incidence of AKI is further increasing because of a growing proportion of elderly and/or multi-morbid patients undergoing cardiac surgery. However, the course of AKI can be highly variable, with either (apparently) complete restoration of kidney function or persistent kidney dysfunction up to 90 days, the latter being termed acute kidney disease (AKD). Finally, in some patients, kidney function remains permanently reduced thereafter or even further declines, a process now recognized as AKI–CKD transition **(1)**

In patients with AKI, the risk for developing CKD is 8.8 times higher as compared with those without AKI. Therefore, AKI, AKD and CKD can be seen as a kind of 'kidney injury continuum', finally resulting in ESKD. Because of the substantial health and socioeconomic burden of AKI including its transition into CKD, it is important to identify patients at increased risk in order

to deploy preemptive strategies for the prevention of AKI and the subsequent loss of kidney function **(19)**.

Therefore the clinical utility of preoperatively determined urinary DKK3 was explored as a predictor of postoperative AKI and subsequent AKI-CKD transition in individuals undergoing elective cardiac surgery. Indeed, it was found that preoperative urinary DKK3 was independently associated with a significantly higher risk of AKI after surgery. Urinary DKK3 predicted the risk of AKI also in patients with normal eGFR before surgery, i.e. in patients with apparently normal kidney function **(1)**

To determine the association between DKK3 and AKI–CKD transition after cardiac surgery, trajectories of eGFR before surgery was built, at discharge from hospital and after long-term follow-up of 820 days after discharge. This approach identified three patterns of eGFR corresponding to patients with no AKI and no loss of kidney function, moderate loss of eGFR after AKI and CKD progression, and severe loss of eGFR after AKI and CKD progression **(1)**

Notably, higher baseline urinary DKK3 was associated with a significantly higher risk for assignment of patients to the trajectory group with severe loss of eGFR after AKI and CKD progression during long-term follow-up. Accordingly, eGFR after long-term follow-up was lower in subjects with higher baseline DKK3. These findings have been validated in the prospective RenalRIP (Renal Effects of Remote Ischemic Preconditioning in Cardiac Surgery) trial, in which patients were randomized to remote ischemic preconditioning (RIPC) or sham procedure before cardiac surgery. Finally, in a *post hoc* analysis of RenalRIP, it was found that RIPC was only associated with a lower risk of postoperative AKI in subjects with pre-operatively elevated urinary DKK3. Further prospective studies are necessary to test whether patients with elevated urinary DKK3 would benefit from specific therapeutic interventions **(1)**

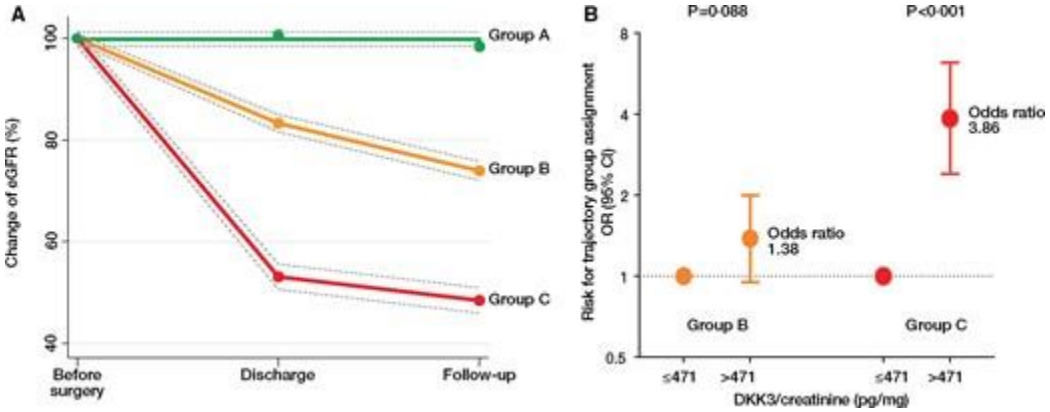

Figure 4: (A) Group-based trajectory modelling of eGFR identifying three distinct eGFR trajectories corresponding to patients with no AKI and no loss of kidney function (Group A), moderate loss of eGFR after AKI and CKD progression (Group B) and severe loss of eGFR after AKI and CKD progression (Group C). Dashed lines indicate 95% CI. (B) Association between urinary DKK3 dichotomized at 471 pg/mg creatinine and eGFR trajectory groups. Urinary DKK3 levels were normalized to urinary creatinine concentrations to account for

dilution of the urine. Results are adjusted for age, gender, body mass index, hypertension, diabetes, smoking status and eGFR at admission **(1)**

In summary, DKK3 represents a novel urinary biomarker of ongoing tubular injury. It identifies patients at risk for short-term CKD progression, regardless of the cause of kidney injury. In addition, high urinary DKK3 levels also signify an increased risk for AKI and for (further) loss of kidney function after an AKI episode as a marker of (subclinical) kidney injury. Further studies will show whether DKK3 may serve as a novel tool to improve the management of patients with known kidney diseases as a personalized medicine approach **(1)**

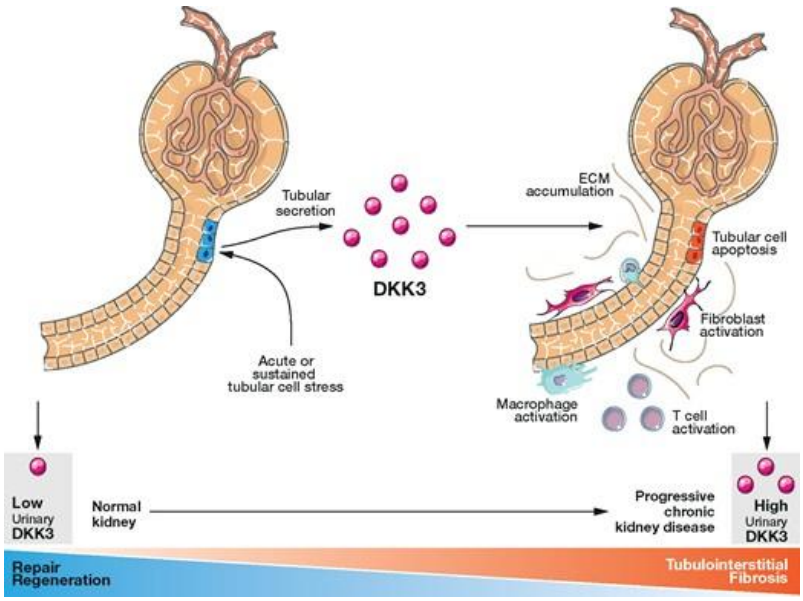

Figure 5: Urinary DKK3 is a biomarker of ongoing renal tubular cell injury, i.e. a renal tubular cell 'stress' indicator within the 'kidney injury continuum'. ECM, extracellular matrix **(1)**

Conclusion

DKK3 promoted renal tubulointerstitial fibrosis through modulation of the canonical Wnt/β-catenin signalling pathway. In clinical studies, increased urinary DKK3 levels identified patients at high risk for short-term CKD progression, regardless of the cause of kidney disease, baseline kidney function and albuminuria. Moreover, increased urinary DKK3 levels are associated with a high risk for acute kidney injury and the subsequent loss of kidney function after cardiac surgery. These findings highlight DKK3 as a mediator of renal tubular cell damage in kidney injury and short-term progression of kidney disease, with potential therapeutic implications

References:

1. Schunk, S. J., Speer, T., Petrakis, I. & Fliser, D. 2020. Dickkopf 3—a novel biomarker of the 'kidney injury continuum'. Nephrology Dialysis Transplantation, 36, 761-7.
2. Kakitapalli, Y., Ampolu, J., Madasu, S. D. & Sai Kumar, M. 2020. Detailed review of chronic kidney disease. Kidney Diseases, 6, 85-91.

3. Zsom, L., Zsom, M., Salim, S. A. & Fülöp, T. 2022. Estimated glomerular filtration rate in chronic kidney disease: a critical review of estimate-based predictions of individual outcomes in kidney disease. Toxins, 14, 127.
4. Chebib, F. T. & Torres, V. E. 2021. Assessing risk of rapid progression in autosomal dominant polycystic kidney disease and special considerations for disease-modifying therapy. American Journal of Kidney Diseases, 78, 282-92.
5. Elshair, H. S. & Elkholy, N. M. 2022. Much more than proteinuria in diabetic kidney disease. Medicine Updates, 9, 106-19.
6. Greenberg, J. H., Abraham, A. G., Xu, Y., Schelling, J. R., Feldman, H. I., Sabbisetti, V. S., et al. 2021. Urine biomarkers of kidney tubule health, injury, and inflammation are associated with progression of CKD in children. Journal of the American Society of Nephrology, 32, 2664-77.
7. Liu, B. C., Tang, T. T., Lv, L. L. & Lan, H. Y. 2018. Renal tubule injury: a driving force toward chronic kidney disease. Kidney Int, 93, 568-79.
8. Tsokos, G. C., Boulougoura, A., Kasinath, V., Endo, Y., Abdi, R. & Li, H. 2023. The immunoregulatory roles of non-haematopoietic cells in the kidney. Nature Reviews Nephrology, 1-12.
9. Obert, L. A., Elmore, S. A., Ennulat, D. & Frazier, K. S. 2021a. A review of specific biomarkers of chronic renal injury and their potential application in nonclinical safety assessment studies. Toxicologic pathology, 49, 996-1023.
10. Hu, H.-H., Cao, G., Wu, X.-Q., Vaziri, N. D. & Zhao, Y.-Y. 2020. Wnt signaling pathway in aging-related tissue fibrosis and therapies. Ageing research reviews, 60, 101063.
11. Rayego-Mateos, S., Campillo, S., Rodrigues-Diez, R. R., Tejera-Muñoz, A., Marquez-Exposito, L., Goldschmeding, R., et al. 2021. Interplay between extracellular matrix components and cellular and molecular mechanisms in kidney fibrosis. Clinical Science, 135, 1999-2029.
12. Giralt, I., Gallo-Oller, G., Navarro, N., Zarzosa, P., Pons, G., Magdaleno, A., et al. 2021. Dickkopf proteins and their role in cancer: A family of Wnt antagonists with a dual role. Pharmaceuticals, 14, 810.
13. Mourtada, J., Thibaudeau, C., Wasylyk, B. & Jung, A. C. 2023. The Multifaceted Role of Human Dickkopf-3 (DKK-3) in Development, Immune Modulation and Cancer. Cells, 13, 75.
14. Schunk, S. J., Speer, T., Petrakis, I. & Fliser, D. 2020. Dickkopf 3—a novel biomarker of the 'kidney injury continuum'. Nephrology Dialysis Transplantation, 36, 761-7.
15. Khttab, R. M. S. A. M. & Allam, H. M. 2023. Plasma Biomarker Dickkopf-3 and its Association with Chronic Kidney Disease. The Egyptian Journal of Hospital Medicine, 91, 4210-4.
16. Zewinger, S., Rauen, T., Rudnicki, M., Federico, G., Wagner, M., Triem, S., et al. 2018. Dickkopf-3 (DKK3) in Urine Identifies Patients with Short-Term Risk of eGFR Loss. J Am Soc Nephrol, 29, 2722-33.
17. Dziamałek-Macioszczyk, P., Winiarska, A., Pawłowska, A., Wojtacha, P. & Stompór, T. 2023. Patterns of Dickkopf-3 Serum and Urine Levels at Different Stages of Chronic Kidney Disease. Journal of Clinical Medicine, 12, 4705.
18. Nadim, M. K., Forni, L. G., Bihorac, A., Hobson, C., Koyner, J. L., Shaw, A., et al. 2018. Cardiac and vascular surgery–associated acute kidney injury: the 20th international consensus conference of the ADQI (acute disease quality initiative) group. Journal of the American Heart Association, 7, e008834.
19. Hapca, S., Siddiqui, M. K., Kwan, R. S., Lim, M., Matthew, S., Doney, A. S., et al. 2021. The relationship between AKI and CKD in patients with type 2 diabetes: an observational cohort study. Journal of the American Society of Nephrology: JASN, 32, 138.