DKK3: PREDICTOR OF ACUTE AND CHRONIC KIDNEY DISEASES

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Abstract:

kidney diseases constitute a common and challenging broad spectrum of disorders that needs more attention to be paid not only by the specialty of nephrology, but also by various medical specialties. Because early recognition and prevention is essential, researchers have been investigating the role of different biomarkers in prediction of kidney injuries to provide early management, and hence better prognosis. Research in this area is of great interest and with a very active research community. Yet, no conclusive opinion about the accuracy of predicting kidney diseases by any of these studied biomarkers was found. There is a rising evidence votes for use of urinary Dickkopf-3 in prediction of AKI, and also as a marker of chronic kidney disease. Recently, Dickkopf-3 gained much attention in the pathophysiology of many disorders of kidney injury. Thus, in this review, we assess the role of DKK3 in prediction of different acute and chronic kidney injury.

Dickkopf (DKK) proteins form an evolutionarily conserved family composed of five secreted glycoproteins, which share two conserved cysteine-rich domains (CRDs), and one divergent member, soggy. The N-terminal CRD is characteristic to the DKK family and is not found in any other vertebrate proteins. The two CRDs are divided by a linker zone, identical to that in DKK1, -2 and -4, but remarkably shorter in DKK3. Through embryogenesis, DKK proteins are co-ordinately expressed in mesenchymal line which lead to kidney development **(1).**

Members of the DKK family have been reported to be modulators of Wnt/ β-catenin pathways which are thought to play an important role in kidney development and kidney disease as well. While DKK1, -2 and -4 have been shown to directly interact with Wnt/β-catenin signaling pathways, DKK3 has not been clearly implicated in Wnt signaling. Some reports argue that DKK3 inhibits while others claim that DKK3 enforces Wnt signaling, depending on the cellular context. Recent reports have suggested that different proteins of the Wnt signaling cascade interact with DKK3 **(2).**

It is believed that DKK3 can act as a tissue-derived immune-modulator affecting the nature and strength of local T cell responses in models of peripheral tolerance, transplantation and autoimmune disease. DKK3 was found expressed during kidney development, which occurs through a mesenchymal-epithelial junction. Because DKK3 can act as an immune-modulator and is expressed in mesenchymal-derived tissue, it is hypothesized that DKK3 may affect chronic inflammatory fibrosing kidney disease **(1).**

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Origin and structure of DKK3

It has been shown that urinary DKK3 levels increase significantly in mice fed an adenine-rich diet, while these levels were undetectable in healthy mice. To determine the DKK3-producing kidney cell type, reporter mice were generated expressing luciferase and mCherry under the regulatory sequences of the Dkk3 gene. In healthy control mice, no luciferase activity was detected by bioluminescence imaging. In contrast, 2 days after unilateral ureteral ligation, luciferase activity was detected within the injured kidney and was not detectable in other compartments of the kidney. Thus, tubular epithelial cells (TEC) appear to be the only source of DKK3 within the kidney **(1).**

Later on, it was noticed that urinary DKK3 concentrations were remarkably higher in patients with CKD than in apparently healthy general population subjects. 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 **(3).**

The expected molecular weight of DKK3 is 38 kDa. However, it has been shown that DKK3 can be essentially glycosylated, increasing its molecular

weight to 6070 kDa. Recently, we found that urine concentrations of DKK3 correlated with albuminuria only in patients with CKD and not in general population subjects. The correlation coefficient for urinary DKK3 and albuminuria was 0.258, indicating that albuminuria accounts for 25.8% of the variability of urinary DKK3 **(4).**

1. DKK3 and acute kidney disease

Acute kidney injury (AKI) is defined as an increase in serum creatinine (SCr) of at least 0.3 mg/dl within 48 hours; a known or suspected increase in SCr greater than 1.5 times baseline within the last 7 days; or a decrease in 6-hour urinary output (UO) below 0.5 ml/kg/h. AKI is a common complication in hospitalized patients and is associated with poor short-term and long-term prognosis **(5).**

Given the impact of AKI on short- and long-term outcomes, understanding the mechanism of AKI is of great importance. The Wnt/ β-catenin pathway is transitorily activated and identified as a protective response that can reduce cellular damage by enhancing tubular repair and regeneration after AKI. Furthermore, Wnt agonists improved renal regeneration and function after renal ischemia-reperfusion (I/R) and reduced inflammation and oxidative stress **(6).**

Therefore, activation of Wnt/ β-catenin signaling can serve as a therapeutic target in AKI. Dickkopf-related protein 3 causes AKI by inhibiting Wnt/ β-catenin signaling. Zhu et al found that β-catenin expression is significantly increased after inhibition of dkk3 expression in I/R-induced cell and rat AKI models. Thus, expression of DKK3 is positively linked to higher incidence of AKI. However, the exaggerated and continuous activation of the Wnt/ β-catenin pathway may contribute to the transition from AKI to chronic kidney disease (CKD) **(7).**

AKI is a well-recognized complication in patients undergoing cardiac surgery. DKK3 has been shown to be an useful biomarker of renal tubular stress in preoperative cardiac patients at risk for AKI and consequent loss of renal function, In a study of 733 patients, preoperative urinary DKK3 was found to remarkably enhance the prediction of AKI risk and post-renal function loss cardiac surgery **(8).**

In a study to investigate the potential use of urinary DKK3 as a biomarker of short-term eGFR loss, urinary eGFR and DKK3 levels were prospectively assessed in 481 patients with CKD of various etiologies and sampled from the general population also compared to samples from patients with confirmed IgA nephropathy.319 Researchers were able to successfully identify patients at high risk for a decrease in eGFR regardless of the cause of kidney damage. Therefore, DKK3 was identified as a potential tool to monitor CKD progression and assess the impact of interventions in patients at short-term risk of eGFR loss beyond what established biomarkers could do **(4).**

In patients with IgA nephropathy, urinary DKK3 levels (normalized to creatinine) were significantly higher in patients with CKD than in the control population, closely followed decreases in eGFR over 12 months were associated with the extent of renal fibrosis and a significantly improved prediction of eGFR decrease and disease progression compared to urinary albumin levels alone. In addition to urinary levels, elevated plasma levels of DKK3 have been found to be associated with progression of kidney graft-versus-host disease, sclerosis, and higher mortality **(9).**

DKK3 also appears to be important in the progression of kidney disease in animals. Using DKK3-deficient mice, tubular damage and renal interstitial fibrosis were significantly reduced compared to wild-type mice after unilateral ureteral ligation and in a mouse adenine nephropathy model. This study also used antibody-mediated blockade of DKK3 to induce similar produce results. Urinary levels of DKK3 in rodents follow disease progression, tubular atrophy, and interstitial fibrosis. In a mouse adriamycin nephropathy model, it was noticed that DKK3 expression was up-regulated in the tubular epithelial and interstitial tissue **(10).**

Altogether, these results propose that DKK3 could be a vital diagnostic marker for both AKI and CKD associated with tubulointerstitial fibrosis. DKK3 is just beginning to be investigated in toxicology studies in rodents and non-rodents, so it remains to be determined whether this potential biomarker for predicting and monitoring the progression of chronic kidney disease will be successful in non-clinical studies, but since the biology of Da der Wnt signaling pathway is similar in humans and animals, the future of this analyte is bright. In humans, an ELISA test is available that appears to cross-react with most species of laboratory animals, although other immunoassays and mass spectrometry have also been used for the analysis of urine and plasma DKK3 **(9).**

In summary, DKK3 is a stress-induced profibrotic tubular epithelium-secreted glycoprotein that may be a useful marker of persistent tubular injury and progressive tubulointerstitial fibrosis, as it plays dual roles in promoting acute repair/regeneration and facilitating progression to CKD **(11).**

1.1. Contrast-induced acute kidney injury (CI-AKI)

Contrast-induced acute kidney injury (AKI), known as contrast-agent-induced AKI (CI-AKI) or contrast-agent-induced nephropathy (CIN), is defined as renal dysfunction occurring 24/72 hours after intravascular injection of X-ray contrast media (CM) in the absence of an alternative etiology. It is usually a non-oliguric, asymptomatic, and transient decrease in renal function that generally occurs within 24 hours of contrast administration, usually peaks on days 3 to 5, and returns to baseline within

10 to 14 days. The incidence of AKI has increased over the past decade, likely due to the aging population, which has led to an increase in several co-morbidities such as non-steroidal anti-inflammatory drugs, chemotherapy drugs, and intravenous (IV) contrast agents **(12).**

The use of CM has increased in recent years due to an increase in X-ray procedures, coupled with an aging population already suffering from diabetes and cardiovascular/kidney disease (including chronic kidney disease, hypertension, hypotension, advanced congestive heart failure). CI-AKI is a common cause of hospital-acquired renal failure, accounting for 12% of all cases **(13).**

In volunteers who underwent cardiac surgery, preoperative urinary DKK3 concentrations had a prognostic value for the development of postoperative AKI. In this way, DKK3 may be able to identify individuals at increased risk who could benefit from preventive measures. The results of this prominently published study raise the question of whether this might also apply to other clinical situations associated with the risk of AKI of other origins. In addition, the sensitivity of DKK3 in predicting AKI has not been defined. Heart surgery can result in severe tubular damage. Also, is DKK3 able to identify subjects who will develop milder forms of AKI? Although the controversy surrounding the effect of contrast media on renal function is still ongoing, it is generally accepted that in most cases the effect on renal function is rather small **(8).** Therefore, contrast-induced AKI (CI-AKI) may be a good model to examine whether DKK3 is able to predict even a slight deterioration in glomerular filtration rate (GFR) **(14).**

Pathophysiology of CI-AKI

The effects of CM leading to AKI are not fully understood, although two main mechanisms are believed to be involved: direct cellular toxicity and effects on renal hemodynamics **(15).**

The direct toxic effects of CM have been studied in a variety of cells, including renal epithelial and mesangial cells. The functional and structural changes observed as a consequence of CM action included: cell death, a decrease in cell viability; and an increase in brush border and lysosomal enzyme activity; cellular DNA fragmentation; down-regulation of signaling molecules involved in cell survival, such as Akt, and up-regulation of signaling molecules involved in cell death, such as the p38 and c-Jun N-terminal kinase members of mitogen-activated protein kinases **(16).**

Scientists believe that CM could initiate release of the vasoconstrictors such as endothelin-1 and adenosine which might lead to decreased blood flow and thus contribute to hypoxic conditions in the renal parenchyma **(16).** The hypoxic conditions then can lead to the production of reactive oxygen species (ROS) that can have deleterious effects within cells themselves **(17).** The reaction between the ROS superoxide anion with nitric oxide lead to the even more powerful oxidant, the peroxynitrite anion. Application of a recombinant manganese superoxide dismutase in vivo to rats going through treatment with the high-osmolarity CM diatrizoate resulted in an improvement in glomerular filtration rate (GFR) and a reduction in histological damage **(18).**

Because the clinical features and management of CI-AKI are the same as for AKI due to other causes, the biomarkers studied to predict early diagnosis of other types of AKI can also be used to predict CI-AKI **(13).**

The use of contrast media increases the risk of worsening renal function in patients with pre-existing renal impairment. eGFR < 60 mL/min/1.73 m2 on coronary angiography, eGFR < 30 mL/min/1.73 m2 on transvenous contrast-enhanced CT is associated with the risk of CIN. Nevertheless, reports on deteriorating renal function as a long-term prognosis of CIN are limited. The risk of acute kidney injury after contrast administration is also determined by factors related to the patient and the procedure itself. Clinical factors that increase the risk of CIN include pre-existing renal dysfunction, diabetes mellitus in the presence of pre-existing renal dysfunction, advanced congestive heart failure, intravascular volume depletion, administration of large amounts of contrast media, and use of high-osmolar contrast media **(19).**

In 2018, the Japan Society of Nephrology, the Japan Society of Radiology, and the Japan Society of Cardiology jointly developed the guideline on the use of iodinated contrast media in patients with renal disease. The guidelines aim to prevent the occurrence of contrast media-induced renal dysfunction, to standardize methods of assessing renal function for patients using contrast media, and to optimize the use of contrast media **(20).**

However, the guidelines do not give a clear statement on the standardization of renal function assessment after contrast medium testing, on the assessment of long-term effects on renal function and on the differentiation from other complications that impair renal function. **(19).**

1.1.1. Biomarkers of CI-AKI

In some cases, contrast-induced AKI is severe AKI with oliguria (< 400 mL/24 h) requiring dialysis. Mortality is high in these patients. It is likely that kidney damage starts immediately after administration of CM and that sensitive early biomarkers could detect kidney damage very soon, and to this end, great efforts have been made in recent years to identify early, specific biomarkers to detect an early to enable diagnosis of AKI and hopefully improve patient outcomes **(21).**

The term biological marker has been defined as any substance, structure, or process that can be estimated in the body or its products and affect or predict the

incidence of outcome or disease. The National Institutes of Health Biomarkers Definitions Working Group defines a biomarker as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacological responses to a therapeutic intervention" **(22).**

A desirable characteristic of any biomarker is that it is sensitive, quantifiable, and can be analyzed quickly to enable timely clinical decisions. In addition, it would also be beneficial if the biomarker was able to provide prognosis and verify the effectiveness of a therapy. In this regard, knowledge of the mechanism or pathophysiology of the disease state is important to identify biomarkers associated with the disease, which would provide information about disease progression and the effectiveness of any therapy, as evidenced by changes in levels of biomarkers. The urgency for new biomarkers of kidney damage is underscored when one considers that for a significant measurable change in serum creatinine it is possible that 50% of the nephrons have already been injured **(23).**

The biomarkers examined can be an expression of renal dysfunction, i.e. an alteration in glomerular filtration (e.g. serum creatinine, microalbumin and Cys-C) or due to altered tubular function (e.g. N-acetyl--d-glucosaminidase [NAG]) or upregulated proteins (eg, kidney damage molecule-1 [KIM-1], neutrophil gelatinase-associated lipocalin [NGAL], and IL-18) resulting from kidney damage **(24).**

Various serum and urine biomarkers have been detected to date, but there is uncertainty regarding their clinical value. Several CI-AKI definitions and different study populations preclude a direct comparison of different biomarkers. A large body of evidence supports the use of urinary neutrophil gelatinase-associated lipocalin (NGAL), however, little is known about the efficacy of other potential urinary biomarkers as early CI-AKI biomarkers, particularly in patients with preserved basic renal function **(25).**

Urinary interleukin 18 (IL-18), kidney injury molecule type 1 (KIM-1)6 and liver fatty acid-binding protein (L-FABP) have been evaluated as potential disease markers, but to date none of the studies have demonstrated the superiority of either single marker for CI-AKI prediction **(26).**

2. DKK3 and Chronic kidney disease

Chronic kidney disease (CKD) is defined as decreased kidney function characterized by a GFR less than 60 mL/min per 173 m2, evidence of kidney damage, or both, lasting at least 3 months, regardless of the underlying cause. The final and most common pathologic consequence of CKD is renal fibrosis, which is characterized by fibroblast proliferation, endothelial mesenchymal transition (EMT), and extracellular matrix (ECM) accumulation. Dickkopf-related protein 3 accelerates renal fibrosis via Wnt signaling. The capability of DKK3 to adjust Wnt signaling is controversial and relies on the tissue context **(1).**

It is evident thatDKK3 promotes renal fibrosis by augmenting activation of Wnt signaling. DKK1 is known to be an inhibitor of canonical Wnt/-catenin signaling. Lipphardt et al found that DKK3 activates Wnt signaling by counteracting the antagonistic effects of DKK1 binding to LRP5/6. Interestingly, fibroblast sensitivity to DKK3 increased significantly at lower concentrations of DKK1, suggesting that DKK1 plays a dominant role and partially antagonizes Wnt signaling at sites distant from the dysfunctional endothelial cells that secrete DKK3. Endothelium-secreted DKK3 has more influence than DKK1 at sites closest to dysfunctional endothelial cells, such as pericytes **(10).**

Therefore, interstitial fibroblasts may be more affected by DKK3 secreted by the epithelium, which can transform fibroblasts into myofibroblasts and lead to renal fibrosis. In addition, Federico et al also found that DKK3 mediates tubular atrophy and interstitial fibrosis by activating Wnt signaling. They found that low expression of DKK3 improves renal tubular atrophy and reduces interstitial matrix accumulation in two mouse models of renal fibrosis by decreasing the activation of Frizzled receptors **(1).**

2.1. DKK3 and autosomal dominant polycystic kidney disease

Autosomal dominant polycystic kidney disease (ADPKD) is the most common monogenic kidney disease worldwide; affecting one in 5001,000 births. The age-dependent focal development of renal cysts is unique to ADPKD. Generally, few renal cysts are clinically detectable in the first three decades of ADPKD; yet, thousands of renal cysts of various sizes can be found in most ADPKD by the fifth decade **(27).**

Progressive cyst expansion with age leads to massive enlargement and distortion of the normal architecture of both kidneys in most patients, ultimately leading to ESRD. ADPKD is also associated with a high risk of heart valve disease and abnormalities in glucose and lipid metabolism **(27, 28).** However, the mechanism that modulates kidney disease progression in ADPKD is poorly understood. Genetic variability in DKK3 may be associated with ADPKD. Liu et al reported that that three single nucleotide polymorphisms at the DKK3 gene locus has a remarkable association with eGFR in ADPKD. The SNP rs3750940 shows the strongest association with eGFR in ADPKD (corresponding to 1.4% of the total variance). Wnt signaling is down-regulated by DKK3 and may be responsible for ADPKD **(29).**

2.2. DKK3 and idiopathic membranous nephropathy

In recent years, idiopathic membranous nephropathy (IMN) has increased due to development of autoantibodies, anti-phospholipase A2 receptor and anti-thrombospondin type I domain with 7A on podocytes. Establishment of circulating immune network complexes and development of autoantibodies have drawn much attention to autoreactive immune cells against the kidney, both innate and adaptive **(30).** The auto-inflammatory reactions in the IMN lead to a dysfunction of the glomerular cells. Therefore, the mechanisms that mediates the immune system hugely contribute to development of idiopathic membranous nephropathy. DKK3 can prevent IMN by altering T cell polarization **(31).**

Since their discovery, the anti-PLA2R and anti-THSD7A autoantibodies promote a paradigm shift in IMN from a histological to a pathophysiological pattern and alter our empirical treatment by preventing antibody production **(32).** T cells, a crucial factor in the immune response, perform immune homeostasis and tolerance by directing the release of cytokines such as IFN and IL-10, the promotion of B cells, and the recruitment of macrophages, neutrophils, and natural killers (NK) support cells and other subsets of T helper cells. A lack of tolerance facilitates the development of autoantibodies and induces inflammation. Ultimately, T cell-derived cytotoxicity leads to tissue damage, particularly in the kidney in IMN **(31).**

Federico et al reported that low expression of DKK3 supports the exacerbation of the experimental autoimmune response in which T cell polarization induced by a rise in IFN-producing T cells was observed in the central nervous system. In addition, DKK3 deficiency increased the number of CD3-positive T cells in the kidneys, accompanied by increased levels of IFN- and TNF-producing CD4+ and CD8+ T-cells **(1),** and exogenous DKK3 reduced CD8 T cell reactivity. These results suggest that DKK3 can downregulate the IMN by affecting T cell polarization and that reducing expression of the IFNDickhead-related protein 3 can attenuate the IMN by altering the fate and function of B- Cells modulated **(33).**

B cell imbalance in immune response is considered to be the main cause of autoimmune diseases, resulting in neglected presentation of autoantigens, production of autoantibodies and impairment of cytokine secretion **(31).** A high percent of B lymphocytes in IMN has been reported. Recent reports showed that inhibition of B cell proliferation and development of pathogenic antibodies effectively alleviated the progression of IMN **(34).**Therefore, the stability and development of B cells plays an essential role in the pathogenesis of IMN. Julia Ludwig and colleagues reported that the composition of the B-cell compartment is altered in DKK3-deficient mice, in which DKK3 is able to alter the development and maintenance of B-cells.

B2 cell development was suppressed in adult DKK3-deficient mice at the pre- and immature B-cell stage, contributing to a reduced number of follicular B-cells, which represent the majority of B-cells in the body **(35).**

Furthermore, DKK3 disrupted the self-preservation of peripheral B1 cells by reducing B1 cell survival and proliferation. In addition, DKK3-deficient mice illustrated a remarkable high expression of the cytokine IL-10, which is unexpectedly increased in the IMN. Hence, DKK3 is an important regulatory protein for the evolvement of a normal B cell compartment. Overall, DKK3 may be a potential therapeutic target in the treatment of IMN because it alters T-cell polarization, maintains B-cell development and function, and decreases cytokines released by T-cells and B-cells. However, there are few studies on the role of DKK3 in IMN **(35).**

2.3. DKK3 and IgA nephropathy

The association between urinary DKK3 and tubulo-interstitial fibrosis was evaluated in a cohort of patients undergoing diagnostic renal biopsy at the University Hospital Innsbruck, Austria, and in renal biopsy specimens from supportive versus immunosuppressive therapy for the treatment of study participants with progressive IgA nephropathy (IgAN) before study inclusion **(36).**

Interestingly, it was found that elevated urinary DKK3 concentrations were significantly associated with higher grade tubulo-interstitial fibrosis in biopsy specimens from both patients with primary glomerular disease and patients with primary interstitial disease **(37).**

In the Care For Home study, urinary DKK3 levels were significantly and independently associated with a decrease in eGFR over the following 12 months after adjusting for a variety of clinical parameters, including baseline eGFR and albuminuria **(37).**

These results were confirmed in the STOP-IgAN study, in which DKK3 > 1000 pg/mg urinary creatinine during the 6-month run-in period was independently associated with a mean 12.2% decrease in eGFR. For STOP-IgAN, adding urinary DKK3 to a model that included age, gender, body mass index, systolic blood pressure, eGFR, and albuminuria increased integrated discriminatizon improvement, net reclassification improvement (NRI), and c-statistic for predicting >0 and significantly >5% decrease in eGFR during the run-in period. For example, the area under the curve for predicting a >5% decrease in eGFR increased significantly from 0.68 to 0.81 with an NRI of 0.29 **(37).**

Notably, in a previous publication of the STOP-IgAN study group, neither NGAL, KIM-1,

calprotectin nor [TIMP2]*[IGFBP7] were linked to progression of IgA nephropathy. During the upcoming first 6 months of the treatment phase, a rise in urinary DKK3 concentration was related to a significant decline in eGFR, while a stable or decreasing urinary DKK3 value indicates a more favorable course of renal function. This result was independent of the randomization to the treatment arms. These findings underscore urinary DKK3 as a biomarker of short-term CKD progression, which may be of importance to nephrologists, particularly for monitoring therapies that slow or even prevent progression. Assessing short-term GFR loss is a different approach than predicting long-term CKD prognosis by considering predefined renal endpoints such as ESRD or 40% GFR decline after several years.

The latter gives a risk estimate of how many patients will reach a renal endpoint, while urinary DKK3 indicates a short-term loss of renal function in the individual patient **(38).**

The association between urinary DKK3 and the predefined renal endpoints mentioned above needs to be determined in future studies. In both cohorts, the CARE FOR HOME study and the randomized STOP-IgAN study, changes in urinary DKK3 levels were independently associated with changes in eGFR, even after adjustment for albuminuria. In addition, the urinary DKK3 also predicted the decline in renal function in patients with normal albumin excretion rate. This indicates that albuminuria/proteinuria and urinary secretion of DKK3 may not be related to the same pathophysiological mechanisms. Further studies are therefore warranted to investigate the mechanisms of renal disease progression in non-proteinuric CKD **(39).**

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