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EDITORIAL

Will osteopontin bridge the gap towards clinical application in chronic kidney disease?

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Chronic kidney disease (CKD) substantially affects global health, affecting ∼10% of adults and leading to 1.2 million deaths and 28 million lost life years each year [1]. In the coming years, CKD will be among the fastest rising causes of death, and is anticipated to be the fifth leading cause of death by the year 2040 [2]. Being able to early identify the individuals at highest risk of developing kidney failure beyond conventional biomarkers like creatinine or albuminuria, comorbidities or validated risk prediction tools (such as the Kidney Failure Risk Equation) is a key research priority, as this would allow the implementation of corrective pharmacological strategies. In this issue of *Nephrology Dialysis Transplantation*, Steinbrenner *et al.* address the potential of serum osteopontin as a biomarker for kidney function, kidney damage, and kidney failure [3].

OSTEOPONTIN AND THE KIDNEY

Osteopontin is an extracellular protein predominantly expressed in the thick ascending limb of the loop of Henle and the distal nephron. Its main physiological functions include the regulation of monocyte-macrophage recruitment by acting as a secreted adhesive molecule and cytokine, and the regulation of biomineralization processes in the body [4]. Being part of the SIBLING family of secreted glycoproteins, its role as a linking protein is underlined by the suffix –pontin, derived from the Latin word for bridge (*pons*). Although its function in the healthy kidney is not fully understood, osteopontin has been implicated in tubulogenesis [4]. Remarkably, osteopontin protein expression in the healthy kidney is low, and knockout mice do not have a kidney phenotype [5, 6]. However, during kidney damage, osteopontin is strongly upregulated in the kidney, and is present in substantially elevated concentrations in both blood and urine [7]. One mechanistic explanation is that it mediates early interstitial macrophage influx, providing a crucial contribution to interstitial inflammation and, subsequently, fibrosis [6]. Indeed, animal experiments in the unilateral ureteral obstruction (UUO) model of kidney fibrosis demonstrated reduced interstitial early inflammation and less tubulo-interstitial fibrosis in osteopontin knockout UUO mice, as compared with wild-type UUO mice [6]. At the same time, a protective role has been proposed for osteopontin, reducing cellular damage through the inhibition of nitric oxide and reactive nitrogen species [5]. In line, depletion of osteopontin from the culture medium by a neutralizing antibody enhanced apoptosis in rat tubular epithelial cells [6].

Although the role of osteopontin in the pathophysiology of progressive CKD has not been fully elucidated, previous studies have consistently demonstrated higher levels in serum, plasma, or urine in groups of patients with various kidney diseases, including minimal change disease, focal and segmental glomerulosclerosis, membranous nephropathy, lupus nephritis, and diabetic nephropathy as well as in kidney transplant recipients with allograft rejection [7]. In IgA nephropathy, findings have been contradictory as not all studies demonstrated clear differences between IgA nephropathy patients and healthy individuals and osteopontin levels did not always correlate with clinical data or pathological findings [7]. In patients with diabetes, a higher plasma or serum osteopontin level has been consistently linked with an increased risk of the development of diabetic nephropathy and worse kidney function (reviewed in [7]). Of note, animal studies also demonstrated increased osteopontin expression in mice with diabetic nephropathy, and osteopontin knockout mice were protected from diabetes-induced albuminuria and mesangial expansion [8]. Altogether, preclinical and clinical studies suggested a role for osteopontin in CKD, although longitudinal data in CKD patients had been missing.

OSTEOPONTIN AND CKD PROGRESSION

In this issue of *NDT*, Steinbrenner *et al.* report an observational study evaluating the association between serum osteopontin and cross-sectional kidney function (eGFR) and kidney damage (albuminuria), as well subsequent risk of kidney failure in a large cohort of CKD patients from the German CKD (GCKD) study [3]. The study population consisted of patients with an eGFR 30–60 ml/min/1.73 m^2 or an eGFR >60 ml/min/1.73 m^2 and increased albuminuria (>300 mg/g creatinine) or proteinuria (>500 mg/g creatinine). This is the largest clinical study in CKD patients evaluating correlates of osteopontin. The main findings are that serum osteopontin levels are strongly associated with eGFR and albuminuria in cross-sectional analyses, and independently of these classic biomarkers, osteopontin was consistently associated with the risk of death and kidney failure. However, osteopontin did not improve the performance of models including established risk equations for kidney failure, including the Kidney Failure Risk Equation.

Strengths of the study include the large sample size and the patient population with a broad range of kidney function and damage. This helps to refute previous observations from smaller studies regarding risks being mediated by inflammation. The validated endpoints, based on a standardized, distinct event adjudication catalogue, are also a strength that contributed to the robustness of the study. Finally, the disease-specific subgroup analyses provided additional insights and seem to point towards a stronger association of osteopontin with outcomes in patients with diabetic kidney disease.

The lack of ostepontin's prognostic value beyond classic risk models challenges the promise of osteopontin as a biomarker for kidney failure in clinical practice. Given the role of osteopontin in biomineralization and CKD-metabolic bone disorder (CKD-MBD), and the role of these in the genesis and complications of CKD progression, we see as a limitation the lack of information and adjustment for serum calcium, phosphate, and parathyroid hormone. From an aetiological point of view, it remains unclear whether higher serum osteopontin level reflects more advanced CKD-induced metabolic deregulation, which in turn is the correlating factor with kidney failure risks.

WHAT DOES IT TAKE FOR A GOOD BIOMARKER?

Do the results from Steinbrenner *et al.* put an end to the quest for osteopontin as a promising biomarker of CKD progression? In our view, osteopontin meets some of the basic requirements for a good biomarker [9]: it is present in peripheral body tissue and/or fluid; it is easy to quantify in assays that are affordable and robust; and its concentrations are associated with kidney damage. Yet, beyond these basic criteria, very few biomarkers have additional prognostic value over and above eGFR and albuminuria [10], and osteopontin may be one of those. Furthermore, it remains unclear what to do with patients with high osteopontin levels as directed anti-osteopontin therapies are, to our knowledge, not available. If biomarkers cannot be specifically targeted, this is a clear impediment for their clinical application [11].

CONCLUSION

Lack of prognostic gain does not necessarily mean that osteopontin is not a true risk factor for kidney failure, but that in clinical practice it may not be better than the biomarkers that we already use. Further research is needed to address whether osteopontin may specifically be able to predict the progression of diabetic kidney disease, as subgroup analyses pointed towards a particularly strong association in this subgroup. Whether the associations are independent of other CKD-MBD biomarkers would also add to the existing literature.

Genetic studies may help discern whether lowering osteopontin levels is 'causally related' with the risk of kidney failure. Another study from the GCKD cohort identified two replicated polymorphisms that were associated with serum osteopontin levels: one close to the *SPP1* gene, encoding osteopontin, and another one that mapped to the *KLKB1* gene encoding prekallikrein, which is processed to kallikrein [12]. Kallikrein, in turn, has been implicated through the kinin-kallikrein system in blood pressure control, inflammation, blood coagulation, cancer, and cardiovascular disease. The *SPP1* gene was not among the 11 loci associated with kidney function decline in a genome-wide association study analysis in >340 000 individuals [13]. The replication of these genetic instruments may be the first step towards adequately designed Mendelian randomization studies exploring the causation behind these observed risks. While currently a bridge too far, osteopontin could be just one step closer to clinical practice.

CONFLICT OF INTEREST STATEMENT

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(See related article by Steinbrenner *et al.* Association of osteopontin with kidney function and kidney failure in chronic kidney disease patients: the GCKD study. *Nephrol Dial Transplant* 2023; 38: 1430–1438)

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