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Authors' Response to "Urinary and Plasma KIM-1 in Chronic Kidney Disease: Prognostic Insights and Remaining Questions"

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We thank Dr. Akcay for his helpful comments regarding our recent article in the *American Journal of Nephrology*, "Plasma and Urinary KIM-1 in Chronic Kidney Disease: Prognostic Value, Associations with Albuminuria, and Implications for Kidney Failure and Mortality" [1]. His letter [2] raises some important mechanistic considerations. First, that Kidney injury molecule 1 (KIM-1) may serve as a link between early tubular injury and subsequent maladaptive repair. Second, that short-term changes in urinary KIM-1 may not consistently predict long-term decline in kidney function. We agree with both observations. Urinary KIM-1 likely reflects acute or initial tubular injury and is less helpful as a biomarker of chronic kidney damage, whereas elevated plasma KIM-1 appears to indicate sustained proximal tubular damage and the maladaptive response [3] that likely contributes to chronic kidney disease (CKD) progression. To the best of our knowledge, our study is the first to measure both urinary and plasma KIM-1 in the same CKD cohort. In highlighting the divergent prognostic associations, with plasma, not urinary KIM-1, being associated with CKD progression, we hypothesize that it is the transition from elevated urinary to plasma KIM-1 that reflects the pathological shift from adaptive to maladaptive response, and this may explain why plasma KIM-1 is a superior predictor of CKD progression.

Dr. Akcay also speculates on why urinary KIM-1 may be more strongly associated with all-cause mortality than CKD progression, proposing that urinary KIM-1 may serve as a systemic health marker rather than a purely renal endpoint predictor. While further research is needed to investigate this, we agree that elevated urinary KIM-1 may reflect a more global inflammatory process. Indeed, in an additional analysis from our study, we have confirmed that several other inflammatory cytokines (including MCP-1 and SuPAR as mentioned by Dr Akcay) are elevated in persons with CKD and are also independently associated with all-cause mortality as well as CKD progression [4].

We agree that KIM-1 offers additional pathophysiological insights beyond established biomarkers in CKD.

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Dr. Akcay points out that elevated KIM-1 levels provide information on interstitial injury and inflammation not captured by creatinine. Given the diverse mechanisms of CKD progression, this ability to capture underlying pathology is crucial and is not unique to KIM-1 alone; it also applies to several other novel biomarkers, a point we have previously made [4, 5]. Despite this, the value of much of the biomarker research in CKD is often judged by its capacity to demonstrate incremental improvements in risk prediction, with pathophysiological insights seen as secondary.

With regard to this point, Dr. Akcay mentions benchmarking novel biomarkers against established risk prediction tools such as the Kidney Failure Risk Equation (KFRE). This was undertaken in our analysis, and we observed modest improvements in the reclassification of kidney failure risk when plasma and urinary KIM-1 were combined in the cohort as a whole. Such small gains in discrimination are common in CKD biomarker studies, largely because existing markers and predictive models like the KFRE already perform so well in diverse and advanced CKD cohorts [6]. As a result, further incremental improvements are difficult to demonstrate in cohorts of advanced CKD, but the true value of novel biomarkers is likely to be to inform a precision medicine approach to CKD and to monitor response to novel therapies, especially in earlier stage CKD.

KFRE is known to perform less well is in early stage CKD. This is because eGFR predominantly drives KFRE risk prediction, which is a significant limitation given the lifelong nature of CKD and the potential benefits of intervening earlier in the disease course. Consequently, we examined the performance of KIM-1 in participants with early CKD (eGFR >45 mL/min/1.73 m^2). In this subgroup, plasma KIM-1 alone demonstrated a much larger improvement in reclassification for CKD progression when compared with KFRE, underscoring its potential to improve risk prediction in earlier disease stages. Additionally, we believe the interaction and correlation with albuminuria that Dr Akcay highlights aligns with preclinical research suggesting that KIM-1 may enhance transport of albumin into the PCT [7]. Thus, elevated KIM-1 may highlight those who could benefit from novel antiproteinuric therapies earlier in their CKD course. In summary, we welcome this insightful response to our paper and agree that KIM-1 holds promise as a biomarker that reflects mechanisms of CKD progression that may be useful to guide precision medicine, though further research is warranted to validate our findings and assess the response of biomarkers to kidney protective therapies.

Conflict of Interest Statement

T.M. and N.V. have no conflicts of interest to declare. M.S. is a full-time employee of AstraZeneca. P.A.K. has previously undertaken lectures and advisory boards for AstraZeneca and UCB, two of the commercial partners of NURTuRE. M.W.T. reports consulting fees and honoraria from Boehringer Ingelheim, honoraria from Bayer and a leadership role in the International Society of Nephrology (Chair of the International Network of CKD Cohorts). Was a member of the journal's Editorial Board at the time of submission.

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Author Contributions

T.M., M.S., P.A.K., M.W.T., and N.V.: contributed to the concept, editing and writing of this letter.

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