RESPONSE TO COMMENT ON TANG ET AL.

The Impact of Carbamylation and Anemia on HbA_{1c}'s Association With Renal Outcomes in Patients With Diabetes and Chronic Kidney Disease. Diabetes Care 2023;46:130–137

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We appreciate Foussard et al.'s interest and comments (1) on our recent article (2) showing that the association between HbA_{1c} and renal outcomes is modified by carbamylation in patients with coexisting diabetes and chronic kidney disease (CKD). They suggest we provide additional information on the impact of carbamylation on HbA_{1c} and its association with renal outcomes across specific CKD stages. We agree that better understanding which CKD patients are most susceptible to carbamylation's modification of HbA_{1c} could have important implications when clinicians consider possible biases of HbA_{1c} in CKD patients.

Patients with later CKD stages are prone to higher carbamylation burden primarily due to more urea accumulation, but the estimated glomerular filtration rate (eGFR) that determines CKD staging does not entirely capture carbamylation load. Our group has shown that serum urea nitrogen level had the strongest association with carbamylated albumin (C-Alb) in CKD patients ($r = 0.55$), more so than eGFR ($r = -0.22$) (3). Nevertheless, of 1,516 patients with coexisting diabetes and CKD in our study, the median C-Alb was significantly higher in CKD stages G4–G5 than in CKD stages G1–G3b (11.4 vs. 7.3 mmol/mol, $P < 0.001$). However, the relationship between C-Alb and HbA_{1c} remained inversely correlated in both CKD groups, G1–G3b ($r = -0.11$) and G4–G5 ($r = -0.19$). When we applied the Cox regression model with interaction terms in the subset of patients with CKD G1–G3b ($n = 1,016$), we found that C-Alb remained an effect modifier of the association between HbA_{1c} and CKD progression (P value for interaction = 0.035) in the fully adjusted model. Taken together, these new data suggest that a competitive relationship between the two posttranslational protein modifications, carbamylation and glycation, is less pronounced but still exists in earlier CKD stages.

The *KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease* (4) suggests that the reliability of HbA_{1c} is high in CKD G1–G3b and progressively worsens with advanced CKD stages (G4–G5) (especially kidney failure treated by dialysis). While such guidance helps provide clinicians with a quick and crude classification system, it lacks insight into the mechanistic underpinnings for such findings that could yield important improvements in monitoring diabetes treatment effectiveness in CKD. We can infer that the reliability of HbA_{1c} is generally greater in earlier CKD stages, and carbamylation burden along with its effect modification on HbA_{1c} is relatively higher in more advanced CKD stages. Nevertheless, our data unequivocally demonstrate that carbamylation still plays an important role and impacts HbA_{1c} and its association with renal outcomes in patients in different CKD stages. Future studies should evaluate whether incorporating carbamylation assessment can improve the risk prediction of HbA_{1c} in patients in different CKD stages.

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