RESPONSE TO COMMENT ON KOSKA ET AL.

Advanced Glycation End Products Predict Loss of Renal Function and High-Risk Chronic Kidney Disease in Type 2 Diabetes. Diabetes Care 2022;44:684–691

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We appreciate the interest in our results (1) showing a strong and independent association of worsening of kidney function with composite advanced glycation end product (AGE) score derived from direct and highly precise measurement of AGE free adducts. The relationship between skin autofluorescence and development or worsening of renal disease described by Borderie et al. (2) or published previously by other groups (3,4) further supports a potential role for products reflected by skin autofluorescence in the development and progression of diabetes kidney disease in type 2 diabetes.

Given the ample evidence of associations between directly measured AGEs and both function and morphological signs of diabetic nephropathy (5–8), it is indeed critical to understand whether therapeutic interventions can modify AGE levels. Unfortunately, we are unable to answer this inquiry in the current cohort of Action to Control Cardiovascular Risk in Diabetes (ACCORD) participants, as the analyses were limited to the baseline samples only. However, we have measured plasma AGE free adduct levels in 424 participants of the Veterans Affairs Diabetes Trial (VADT) at baseline and after 1 year. By study design (9), hemoglobin A_{1c} levels declined substantially more in the intensive glucose-lowering group (median −2.3% [25% of baseline HbA_{1c}] vs. −0.7% [8% of baseline HbA_{1c}]; in the standard group, median HbA_{1c} 6.8% vs. 8.3% at year 1, $P < 0.0001$). Interestingly, the AGE score was not decreased, and indeed was slightly increased, compared with baseline in the intensive group (0.18 units, $P = 0.01$); however, this change was not significantly different from the value of the standard group (0.11 units) ($P = 0.9$). Thus, intensive glucose lowering does not appear to reduce AGE burden at 1-year follow-up in this older population.

Given the long-term nature of AGE accumulation and clearance, we cannot exclude the possibility that a longer duration of glucose lowering is required to reduce overall and plasma AGE burden. Analyses of samples from more recent cohorts will be necessary to determine if newer diabetes medications, which have additional nonglycemic lowering benefits that may alter AGE formation or clearance, may be effective in modifying AGE levels.

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Duality of Interest. P.J.B. is an employee and stockholder of the company PreventAGE Health Care, which performed the analyses of the AGEs used for the study. No other potential conflicts of interest relevant to this article were reported.

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