LETTER TO THE EDITOR

Confirming the causal role of advanced glycation end-products in arterial stiffening

To the Editor We have read with great interest the recent article by Stróżecki et al.[1] In this excellent study, the authors[1] investigated the relationship between plasma levels of advanced glycation end-products (AGEs) and pulse-wave velocity (PWV) (a gold standard method for measuring arterial stiffness). Although they found a significant correlation between AGEs and PWV in patients with chronic kidney disease (CKD), the association between plasma AGE concentration and PWV was insignificant in a multiple linear regression analysis. Although the study[1] provides exhaustive data, and we fully acknowledge their contribution to the field, we believe that some additional comments might be valuable.

AGEs are accumulated in the process of aging, especially in patients with diabetes, thus leading to vascular diabetic complications.[2,3] Moreover, they have been shown to cause oxidative stress and inflammation in diabetes.[2,3] Because AGEs may also suppress protective mechanisms, it seems reasonable to suggest that they could impair insulin secretion and increase the development of insulin resistance, thus playing an important role in the pathogenesis of diabetes.[2] Nonetheless, Forbes et al.[4] reported that plasma insulin levels, markers of inflammation, and oxidative stress, were improved in diabetic patients by reducing AGE levels. Furthermore, high insulin level and insulin resistance could inhibit endothelial nitric oxide synthase and increase the collagen component of the vessel, which stiffens the arterial wall.[5]

Consequently, since there are close associations between AGEs, oxidative stress, inflammation, insulin resistance, and arterial stiffness, we believe that insulin resistance should also be evaluated when assessing the relationship between AGEs and PWV in patients with diabetic nephropathy and CKD.[2-6] Assessment of insulin resistance could help confirm the causal role of AGE accumulation in arterial stiffening.

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Authors' reply We would like to thank Yalçinkaya and Celik[1] for their valuable comments on our study.[2] We appreciate their significant contribution to the ongoing discussion. In our study, a significant positive correlation was found between plasma levels of advanced glycation end-products (AGEs) and pulse-wave velocity (PWV; a measure of arterial stiffness). However, in a multiple regression analysis, PWV was independently associated only with age, diabetes, and systolic blood pressure, but not with AGEs. We concluded that accumulation of AGEs and arterial stiffness are increased in CKD, particularly in patients with diabetic nephropathy; however, the results were not sufficient to confirm the causal role of AGE accumulation in arterial stiffening.

Yalçinkaya and Celik suggest that insulin resistance, AGEs, and arterial stiffness are closely associated, and that insulin resistance should also be evaluated when assessing the relationship between AGEs and PWV in diabetic patients. In fact,

the relationship between insulin resistance and arterial stiffness was documented in CKD patients, even in those without diabetes.[3]

However, our study was not designed to investigate the relationship between insulin resistance and AGE accumulation or arterial stiffness. What is more, the study group of CKD patients with diabetic nephropathy was heterogeneous with respect to underlying diabetes. There were 11 patients with type 1 diabetes and 13 patients with type 2 diabetes (see Table 3 in the original article).[2] All type 1 diabetic patients and most of type 2 diabetic patients with CKD were treated with insulin. For that reason, evaluation of insulin resistance in this population with the glucose clamp technique or homeostatic model assessment would have been difficult to perform and interpret.

We still believe that further studies investigating the role of AGEs in cardiovascular complications will provide new therapies to reduce extremely high cardiovascular risk in diabetic and nondiabetic CKD patients.

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