COMMENTS AND RESPONSES

Low Serum Level of the Endogenous Secretory Receptor for Advanced Glycation End Products (esRAGE) Is a Risk Factor for Prevalent Vertebral Fractures Independent of Bone Mineral Density in Patients With Type 2 Diabetes

Response to Yamamoto et al.

I have recently read an interesting article in *Diabetes Care* (1) that showed that the low serum level of the endogenous secretory receptor for advanced glycation end products (esRAGE) was independently associated with the prevalence of vertebral fractures in patients with type 2 diabetes. I totally agreed with the authors' opinions that bone quality may be more important than bone density in defining the increased risk for fracture in type 2 diabetic patients and that the advanced glycation end product (AGE)–receptor for AGEs (RAGE) system could play a role in impaired bone quality in these patients. However, it seemed unlikely to me that an insufficient amount of esRAGE to counteract AGEs could intensify the binding of AGEs to RAGE and exert harmful effects on bones, thus being involved in the increased risk of vertebral fractures in their patients.

The endogenous soluble form of RAGE (sRAGE) can generate from the cleavage of cell surface full-length RAGE by sheddase or novel splice variants of RAGE (2,3). Most sRAGE is derived from the cleavage of membrane-bound RAGE, while esRAGE is one of the C-truncated splice isoforms of RAGE and only constitutes a small portion of endogenous sRAGE (2,3). Since the interaction of RAGE with the ligands such as AGEs and high-mobility group protein box-1 (HMGB1) promotes the RAGE shedding (3), endogenous sRAGE levels could correlate with high levels of ongoing inflammation in diabetes. Indeed, my colleagues and I, along with others, have found that sRAGE levels are positively rather than inversely associated with circulating AGEs and could reflect tissue RAGE expression in type 2 diabetes (2). Therefore, although exogenously administered sRAGE was shown to block the harmful effects of AGEs in animals by acting as a decoy receptor for AGEs, it is questionable that esRAGE could also exert the same biological effect given that serum levels of esRAGE in humans are 5,000 times lower than needed for the binding to AGEs (2,4). The authors' finding that esRAGE levels were positively rather than inversely correlated with pentosidine further supports the concept that esRAGE levels are not sufficient to eliminate circulating AGEs efficiently in type 2 diabetes. Therefore, decreased levels of esRAGE may be associated with the prevalence of vertebral fractures in type 2 diabetes in unknown mechanisms other than working as a decoy receptor for AGEs.

Since my colleagues and I and others have recently found that sRAGE levels are independently and inversely associated with HMGB1 levels in an apparently healthy population and that sRAGE is absent and HMGB1 levels are higher in diabetic RAGE$^{-/-}$/apolipoprotein E$^{-/-}$ mice (5), esRAGE may protect against vertebral fractures by working as a decoy receptor for circulating HMGB1. Binding affinity of HMGB1 to RAGE is 10 times higher than that of AGEs, whereas serum concentration of HMGB1 is 1,000 times less than that of AGEs (2,5), thus supporting the concept that circulating HMGB1 but not AGEs is a molecular target for esRAGE.

It would be interesting to examine whether high serum levels of HMGB1 and low esRAGE-to-HMGB1 ratio could be more useful markers in evaluating the risk of vertebral fractures in their subjects.

SHO-ICHI YAMAGISHI, MD, PHD

From the Department of Pathophysiology and Therapeutics of Diabetic Vascular Complications, Kurume University School of Medicine, Kurume, Japan.

Corresponding author: Sho-ichi Yamagishi, shoichi@med.kurume-u.ac.jp.

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