Comment on: Selvin et al. sRAGE and Risk of Diabetes, Cardiovascular Disease, and Death. Diabetes 2013;62:2116–2121

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I have recently read an article by Selvin et al. (1) that showed that low plasma levels of soluble circulating receptor for advanced glycation end products (sRAGEs) at baseline were independently associated with the risk of coronary heart disease (CHD) and all-cause mortality during a median of 18 years of follow-up in a community-based population. I totally agree with the authors' opinions that low sRAGE level is a marker of future chronic disease risk and mortality in the generation population. However, I think it unlikely that sRAGE could work as a "sponge" for AGEs in humans and that an insufficient amount of sRAGE to counteract the detrimental effects of AGEs might be involved in the increased risk of CHD and death in their population as AGEs stimulate cell surface expression of RAGE, and sRAGE level is positively *rather than* inversely associated with circulating AGEs in both diabetic and nondiabetic subjects (2). Since sRAGE is mainly generated from the cleavage of cell surface full-length RAGE, whose process is promoted by the engagement of RAGE with the ligands such as AGEs and high mobility group protein box-1 (HMGB1) (2), it is conceivable that sRAGE level could reflect tissue RAGE expression. The fact that sRAGE level is 1,000 times lower than needed for efficiently capturing the circulating AGEs (2) further supports the concept that sRAGE could not work as a decoy receptor for AGEs in humans.

Moreover, in contrast to the authors' present findings, four clinical studies, including three prospective trials, have shown that higher, *not lower*, levels of sRAGE are independently associated with the risk of future CHD, fetal cardiovascular disease, or all-cause mortality in diabetic subjects or older community-dwelling women (2–4). Therefore, clinical significance of sRAGE as a biomarker may differ considerably depending on the patient's background. sRAGE level is independently and inversely associated with HMGB1 value in a general population (5). HMGB1 level is increased in diabetic RAGE$^{-/-}$/apoE$^{-/-}$ mice, while sRAGE is absent in these animals (5). Further, HMGB1 has 10 times higher binding affinity to RAGE, and its serum concentration is 1,000 times less than that of AGEs (2,5). These findings suggest that circulating HMGB1 *but not* AGEs might be a molecular target for sRAGE. It would be interesting to examine whether low sRAGE level is associated with high HMGB1 value and if decreased ratio of sRAGE to HMGB1 could be linked to future chronic disease risk and mortality in their population.

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