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

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Selvin et al. (1) report that, in a community-based population, *lower* levels of soluble circulating receptor for advanced glycation end products (sRAGEs) at baseline were independently associated with risk of diabetes, coronary heart disease, and all-cause mortality during 18 years of follow-up. These findings are challenging since we and others have previously reported that *higher* levels of sRAGE are associated with incident cardiovascular disease and all-cause mortality in type 1 (2,3) and 2 diabetes (4,5).

The reasons for these contradictory findings are not clear. As these studies all used the same sRAGE assay, the possibility that different variants of sRAGE are detected by different assays can reasonably be excluded. Selvin et al. interpreted low sRAGE levels to represent an inflammatory state. However, this seems unlikely as an inflammatory state seems to be essential for the upregulation of RAGE and also for the process of shedding of RAGE by proteinases, such as by ADAM10 and MMP9. The authors also speculated that sRAGE can bind to ligands such as AGEs, thereby acting as a decoy. However, it is very unlikely that sRAGE can act as such because plasma sRAGE concentrations are approximately 1,000 times lower than those of AGEs.

What then explains these contradictory findings? Lower sRAGE levels in blacks compared with whites suggest ethnic differences in sRAGE and thus genetic control. Indeed, in Caucasians, the CT (vs. the CC) genotype of the RAGE polymorphism rs2060700 (Gly82Ser) was associated with lower sRAGE concentrations (2,3). Furthermore, Asians have a higher prevalence of the CT and TT genotypes than Caucasians, which may explain their lower sRAGE levels (6). A high prevalence of CT or TT genotypes in Atherosclerosis Risk in Communities study participants might explain their relatively low sRAGE levels. Although mechanisms where this single nucleotide polymorphism affects plasma sRAGE remain unknown, alteration of N-glycosylation caused by the Gly82Ser polymorphism may induce structural changes in the protein that makes RAGE less vulnerable for the action of proteinases, thereby lowering the concentration of sRAGE but increasing the concentration of RAGE on the cell surface. Upregulation of RAGE on the cell surface without shedding can lead to increased cell activation and low-grade inflammation and subsequently lead to an increased risk of cardiovascular disease. Thus, the nature of the association between sRAGE and cardiovascular disease may depend on genetic background.

We conclude that the nature of the association between sRAGE and health outcomes is unclear and requires further investigation.

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