Serum Levels of Soluble Form of Receptor for Advanced Glycation End Products (sRAGE) May Reflect Tissue RAGE Expression In Diabetes

To the Editor:
I have read two interesting papers about endogenous C-truncated splice isoform of secretory receptor for advanced glycation end products (esRAGE), which were recently published in your journal.1,2 The findings that esRAGE levels are correlated with serum pentosidine and carboxymethyllysine in type 1 diabetes by Miura et al3 are consistent with our and Tan’s previous observations that serum levels of total soluble form of RAGE (sRAGE) were positively, but not inversely, correlated with circulating AGE levels in nondiabetic and type 2 diabetic subjects, respectively.4,5 These observations suggest that endogenous esRAGE or sRAGE levels are not sufficient to eliminate circulating AGEs efficiently in vivo. However, Koyama et al2,5 recently reported in ATVB that decreased levels of esRAGE were associated with comorbidity including the metabolic syndrome and atherosclerosis and with cardiovascular mortality in end-stage renal disease patients. Therefore, it is unlikely that esRAGE protects against these devastating disorders by working as a decoy receptor for AGEs in vivo. Indeed, they also claimed in their article that pentosidine level was positively, but not inversely, associated with esRAGE.

In contrast to the case of esRAGE, circulating sRAGE levels are increased, rather than decreased, in both type 1 and type 2 diabetic patients.4,6,7 Further, the following evidence supports the concept that circulating sRAGE may be elevated in response to serum AGE levels and reflect tissue RAGE expression in diabetes, thereby acting as a negative feedback agent against the AGE-elicited vascular injury: (1) RAGE belongs to the same immunoglobulin superfamily as intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) and that serum levels of soluble forms of ICAM-1 and VCAM-1 are elevated in patients with diabetes by reflecting upregulation of these adhesion molecules in endothelial cells (ECs).8 (2) Angiotensin II increases RAGE mRNA levels in ECs and subsequently stimulates sRAGE formation in vitro. Treatment with telmisartan, an angiotensin II type 1 receptor blocker, not only inhibits the angiotensin II-elicited sRAGE generation by ECs, but also decreases serum levels of sRAGE in patients with essential hypertension.9 (3) AGEs are positive regulators of cell expression of RAGE and that RAGE is upregulated in atherosclerotic plaques in diabetes, diabetic nephropathy, and retinopathy.10-12 (4) Vitreous levels of sRAGE are increased in proliferative retinal diseases by reflecting enhanced RAGE expression in epiretinal membranes of the eyes.12 Moreover, sRAGE levels are positively associated with the presence of coronary artery disease in type 2 diabetes.3 In addition, we have very recently found that serum levels of sRAGE are positively correlated with inflammatory biomarkers such as tumor necrosis factor-alpha (TNF-α) and monocyte chemotactrant protein-1 (MCP-1) in type 2 diabetic patients. Taken together, these observations suggest that the kinetics and role of sRAGE and esRAGE in diabetes could differ and that sRAGE level may become a novel biomarker of vascular injury in patients with type 2 diabetes.

Disclosures
None.


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