Is Elevated Levels of Serum Soluble Receptor for Advanced Glycation End Products Harmful in Cigarette Smokers?

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I congratulate Dr. Biswas for his excellent work published in *Diabetes & Vascular Disease Research* in 2013. We quoted his work in a review by Prasad et al in 2015. He raised a few questions in support of his publication. Here, I would like to respond to his comments.

Advanced glycation end products (AGEs) are a heterogeneous group of molecules formed from nonenzymatic reaction of reducing sugars with amino group of proteins, lipids, and nucleic acids.[1] AGEs interact with its cell receptor RAGE (receptor for AGEs) and activates nuclear factor kappa-B (NF-kB),[2] and generates reactive oxygen species.[3] Activation of NF-kB increases the gene expression of proinflammatory cytokines and cell adhesion molecules.[3–6] RAGE comprises of the transmembrane domain, a highly charged cytosolic tail and an extracellular region. Extracellular domain is the principle site of interaction between RAGE and its ligands. RAGE is expressed in a variety of cells, including, endothelial cells, mononuclear phagocytes, lymphocytes, vascular smooth muscle cells, hepatocytes, glomerular cells, or podocytes and neurones.[7] RAGE is constitutively and inducibly expressed in cells depending upon the type and developmental stage.[8] The RAGE is expressed in a regulated manner in adult life. The interaction of ligand with receptor increases the expression of the receptor itself.[9] Also, there is a positive correlation between serum levels of soluble RAGE (sRAGE) and expression of endothelial RAGE.[10] Membrane-bound RAGE is called full-length RAGE. Besides full-length RAGE, there are two isoforms of c-truncated soluble RAGE called cleaved RAGE (cRAGE) and endogenous secretory RAGE (esRAGE). cRAGE is proteolytically cleavage of full-length RAGE,[11] while esRAGE is alternative splicing from full-length RAGE.[12] Measurement of total sRAGE includes both esRAGE and esRAGE whereas measurement of esRAGE includes only esRAGE. cRAGE is predominant in the serum and constitutes 80% of total sRAGE.[13] sRAGE and esRAGE do not have cytoplasmic and transmembrane domain and circulate in the blood. sRAGE competes with full-length RAGE for ligand binding and function as a decoy. sRAGE can bind RAGE ligands before they interact with full-length RAGE. AGE–RAGE axis has three important players, and since RAGE cannot be measured in humans, a consideration should be given to both AGEs and sRAGE and not only AGEs or sRAGE in the assessment of biomarkers or risk markers. In consideration of this I have suggested that the ratio of AGEs/sRAGE and AGEs/esRAGE should be a risk marker or a biomarker for the disease.[14]

We published an article on the "Role of AGEs and its receptor in the pathogenesis of cigarette smoke-induced cardiovascular disease." [15] We quoted his[16] and others articles in that article. We quoted that cigarette smoking has variable effects on the serum sRAGE, including, decrease, increase, and no effects. His article was the only article that reported an increase in the serum levels of sRAGE. Dr. Biswas commented that studies that reported a reduction in the serum levels of sRAGE did not consider hypertension in the exclusion criteria in selection of patients. This implies that if the other authors had excluded the hypertensive patients the serum levels of sRAGE would have been increased and not reduced. I am in agreement with that comment. We know that there are many confounding factors which should be considered in the selection of patients. For example, the pulmonary function tests should have been performed in patients the so-called healthy smokers. However, I do not disagree with the data reported by others. I have no concern that the levels of sRAGE was higher in smokers than the control healthy subjects in the study reported by Dr. Biswas.[16] Based on the findings of other authors[17–19] that sRAGE is proinflammatory, Biswas et al[16] in their article stated that elevated levels of sRAGE in cigarette smokers is not surprising. These statements imply that sRAGE is proinflammatory. Biswas et al should have measured the levels of AGEs in these patients. May be the levels of AGEs are also elevated in

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smokers, and the elevation of AGEs is greater than the elevation in sRAGE. In fact, serum levels of AGEs are elevated in cigarette smokers.[20] If the ratio of AGEs/sRAGE is higher in spite of an increase in the levels of sRAGE in cigarette smokers compared with controls, then the proinflammatory mediators will be higher than controls, because more AGEs are available to interact with cellular RAGE. The levels of sRAGE are elevated in end-stage renal disease and diabetes and so are the levels of AGEs.[14] The rise in the sRAGE may probably be due to an increase in the levels of AGEs in cigarette smokers.[20] AGEs are known to upregulate the expression of RAGE in various tissues.[21,22] Also, there is a close relation between serum levels of AGEs and endothelial cell RAGE expression.[10]

Biswas et al[16] have quoted the paper of Nakamura et al[17] who reported that there is a significant positive correlation of sRAGE with inflammatory markers, monocyte chemoattractant protein-1, and tumor necrosis factor (TNF)-α in type-2 diabetes and suggested that sRAGE may serve as a biomarker of vascular inflammation. Again serum levels of AGEs were not measured in this study. If levels of AGEs are also elevated and the elevation of AGEs are more than the elevation of sRAGE, then the ratio of AGEs/sRAGE will be greater resulting in release of proinflammatory mediators. The ratio AGEs/sRAGE and not only levels of sRAGE should be a marker for vascular injury.

Bopp et al[18] reported that serum levels of sRAGE are elevated in patients with sepsis. It is possible that levels of AGEs, which were not measured, were also elevated in these patients. In fact, serum levels of AGEs are elevated in patients with septic shock.[23] The ratio of AGES/sRAGE and not sRAGE should have been the marker for sepsis. It has been reported by Yamamoto et al[24] that lipopolysaccharide (LPS) administration to $RAGE^{+/+}$ mice showed higher levels of interleukin 6, TNF-α, and high mobility group box chromosomal protein 1 (HMGB 1) ligand, and mortality compared with $RAGE^{-/-}$ mice. Administration of sRAGE significantly reduced LPS-induced increase in cytokine release both in $RAGE^{+/+}$ and $RAGE^{-/-}$ mice, suggesting that sRAGE may be a therapeutic agent in LPS-induced shock.

The study of Pullerits et al[19] shows that sRAGE has proinflammatory properties in splenic cell culture. They also reported that the severity HMGB 1-induced arthritis is significantly lower in the group of mice treated with sRAGE. Based on these data, they suggested that sRAGE is not only a decoy receptor, but it also has immunomodulating activity of its own. Measurement of proinflammatory cytokines in the blood of mice where sRAGE was administered before HMGB 1-induced arthritis and where sRAGE had a protective effect against arthritis would have shed some light. It would have been interesting to see if the protective effect of sRAGE was associated with decreases in the levels of proinflammatory cytokines.

There are various reports which show that sRAGE has protective effects and reduce the proinflammary mediators. Bucciarelli et al[25] reported that streptozotocin-induced diabetes, accelerated atherosclerosis in apolipoprotein E (apoE)-deficient mice and this was associated with enhanced expression of vascular cell adhesion molecule-1 (VCAM-1), tissue factor, and matrixmetalloproteinase-9 (MMP-9) in atherosclerotic aorta. Treatment of diabetic mice with sRAGE significantly reduced aortic VCAM-1, tissue factor, and MMP-9. Similar findings were reported by Wendt et al[26] in murine model of type-2 diabetes. Kislinger et al[27] have also shown that sRAGE suppressed levels of VCAM-1, tissue factor, and expression of RAGE in aorta of apoE-deficient diabetic mice. The protective effects of sRAGE in neuronal dysfunction and reduction of development of cellular capillaries and pericyte ghosts in experimental diabetic retinopathy have also been reported.[28] sRAGE inhibits retinal leukostasis and retinal barrier breakdown in diabetic mice and this is associated with decreased expression of vascular endothelial growth factor and intracellular cell adhesion molecule-1.[29]

In conclusion, cigarette smoke has been reported to affect the serum levels of sRAGE variably (increase, decrease, or no effect) in humans. A strict inclusion and exclusion criteria should be applied in selecting cigarette smokers for measurement of AGEs and sRAGE. A double blind study with a large number of smokers should be performed. The most important suggestion is that the ratio of AGEs/sRAGE, but not the AGEs or sRAGE alone should be used as biomarker/risk factor for the disease state.

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