What does Cigarette Smoking do to the Circulating Level of Soluble Receptor for Advanced Glycation End Products?

Subrata Kumar Biswas, MBBS, MD, PhD[1]

[1] Department of Biochemistry, Bangabandhu Sheikh Mujib Medical University (BSMMU), Shahbag, Dhaka, Bangladesh

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Address for correspondence Subrata K. Biswas, MD, PhD, Department of Biochemistry, Bangabandhu Sheikh Mujib Medical University (BSMMU), Shahbag, Dhaka 1000, Bangladesh (e-mail: su.biswas@yahoo.com).

The receptor for advanced glycation end products (RAGEs) is a cell surface receptor of immunoglobulin superfamily. The RAGE expresses highly in the lung tissue, and the lung is directly exposed to cigarette smoke in smokers. Cigarette smoke has been shown to increase RAGE expression and to induce the formation of advanced glycation end products (AGEs).[1,2] However, what the cigarette smoking does to the circulating level of soluble RAGE (sRAGE), a splice variant of full-length RAGE or a shedding/cleavage product of membrane-bound RAGE, is not yet completely known. In this context, I read the review by Prasad et al[3] in the *International Journal of Angiology* with great interest, and I would like to thank the authors for extensively citing our previous article[4] in their review. Prasad et al[3] found various reports[4–8] showing reduced, elevated, or unchanged levels of sRAGE in smokers, but they concluded that cigarette smoke reduces sRAGE level.[3] However, I think it is very important to carefully scrutinize those reports[4–8] before concluding on the status of sRAGE in smokers.

In their review, Prasad et al[3] cited three articles[5–7] that showed reduced sRAGE levels in smokers. Among them, Gopal et al[5] studied the association of plasma sRAGE with lung function impairment in chronic obstructive pulmonary disease (COPD) and found that sRAGE level is significantly lower in ex-smokers compared with never smoker controls. This study compared 44 ex-smokers (mean age: 61 $\pm$ 5.4 years) with only 11 never smoker controls (mean age: 58 $\pm$ 5.9 years) without giving any information about blood pressure, an important negative confounder of sRAGE, of the study subjects. Most importantly, Gopal et al[5] did not compare the sRAGE level of healthy current smokers with that of nonsmokers or never smokers. In the second study, Iwamoto et al[6] studied the association of plasma sRAGE with progression of airway disease and found significantly reduced level of sRAGE in smokers without COPD compared with nonsmokers. This study compared 32 nonsmokers (mean age: 56 $\pm$ 9.1 years) with 212 smokers (mean age: 52.1 $\pm$ 8.8 years; current smoker 79%, ex-smoker 21%; history of smoking $>$ 10 years) but did not give blood pressure of the study subjects.[6] Finally, Yokota et al[7] studied the association of sRAGE with leukoaraiosis in acute stroke patients. They studied 482 hypertensive acute stroke patients (mean age: 71 years) and found that the group with the highest quartile of sRAGE had more number of nonsmokers and fewer number of current smokers compared with the group with the lowest quartile of sRAGE. They also showed that smoking habit was negatively associated with sRAGE in the acute stroke patients.[7] Contrary to these three studies, Prasad et al[3] also cited the article by Smith et al[8] who did not find any difference in sRAGE level between never smokers ($n = 28$) and ex-smokers ($n = 14$) with a median age of 61.6 years while studying the sRAGE level in COPD patients. Of note, none of these studies[5–8] primarily aimed at identifying sRAGE status in cigarette smokers, and therefore the study design and the characteristics of the study subjects are not supportive or convincing enough to conclude on the status of sRAGE in smokers.

Prasad et al[3] also cited our article[4] on the association of sRAGE with cigarette smoking where we specifically aimed to compare sRAGE levels between cigarette smokers and nonsmokers. We studied 98 relatively young (mean age: 34.1 $\pm$ 8.5 years) otherwise healthy nonsmokers ($n = 53$) and current smokers ($n = 45$) who were similar in terms of age, sex (only male subjects were studied), systolic and diastolic blood pressure, body mass index, fasting glucose, and estimated glomerular filtration rate. To eliminate the effect of common confounding variables on sRAGE we excluded subjects with diabetes, obesity, hypertension, renal/hepatic impairment, and regular drug users.[4] This study for the first time showed a significant elevation of sRAGE in cigarette smokers compared with nonsmokers, a strong correlation between sRAGE and number of cigarettes smoked per day and an independent association of sRAGE with the

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smoking habit.[4] This finding may appear to be contrary to the protective nature of sRAGE, however, it is scientifically explainable in various ways. First, increased sRAGE level in relatively young, otherwise healthy smokers may result from a compensatory response to increased smoking-induced AGE formation. However, such compensatory response may not persist or even may become opposite in older subjects with a very long history of smoking and in the presence of confounding conditions/diseases. This may be a reason why several reports found reduced sRAGE levels in smokers.[5–7] Second, the sRAGE level may rise in smokers due to the fact that the cigarette smoke-induced increased RAGE expression is likely to be associated with increased shedding of membrane-bound RAGE and/or increased expression of splice variants of full-length RAGE. Third, the sRAGE may act as a biomarker of inflammation and thus may become elevated in cigarette smokers. In fact, Nakamura et al[9] previously found significant positive correlation of sRAGE with inflammatory markers, monocyte chemotactic protein-1, and tumor necrosis factor-α, in type 2 diabetes mellitus and suggested that sRAGE may appear as a biomarker of vascular inflammation in diabetes. In addition, the sRAGE level was found elevated in patients with sepsis and in human volunteers with lipopolysaccharide-induced inflammation.[10,11] Furthermore, sRAGE itself appeared to be proinflammatory and chemotactic molecule in an experimental study.[12] Based on these findings, we stated in our previous article[4] that 'Thus, considering sRAGE as a pro-inflammatory molecule, the finding of elevated levels of sRAGE in cigarette smokers is not surprising." In fact, we had not had the opportunity to measure AGE, inflammatory markers or shedding/splicing status of RAGE in that article.[4] Thus, we had not stated that "sRAGE is pro-inflammatory," whether it is scientifically sound or not.

Therefore, based on the existing evidence it is at least not appropriate in my opinion to conclude that cigarette smoking reduces the circulating sRAGE level. Further studies with adequate sample size and minimum interference of confounding factors are needed to explore the sRAGE status in cigarette smokers.

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