

Low Levels of Serum Soluble Receptors for Advanced Glycation End Products, Biomarkers for Disease State: Myth or Reality

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Abstract

Advanced glycation end products (AGEs) interact with the receptor for AGEs (RAGE) on the membrane and induce deleterious effects via activation of nuclear factor kappa-B, and increased oxidative stress and inflammatory mediators. AGEs also combine with circulating soluble receptors (endogenous secretory RAGE [esRAGE] and soluble receptor for RAGE [sRAGE]) and sequester RAGE ligands and act as a cytoprotective agent. esRAGE is secreted from the cells and is a spliced variant of RAGE. The sRAGE on the other hand is proteolytically cleaved from cell surface receptor via matrix metalloproteinase (MMPs). sRAGE is elevated in type 1 and type 2 diabetes and in patients with decreased renal function. Serum levels of sRAGE are reduced in diseases including coronary artery disease, atherosclerosis, essential hypertension, chronic obstructive lung disease, heart failure, and hypercholesterolemia. Serum levels of AGEs are elevated in patients with coronary artery disease and atherosclerosis. However, the increases in serum AGEs are very high in patients with diabetes and renal disease. There is a positive correlation between serum levels of AGEs and RAGE and sRAGE. The elevated levels of sRAGE in patients with diabetes and impaired renal function may be due to increased levels of MMPs. AGEs increase in the expression and production of MMPs, which would increase the cleavage of sRAGE from cell surface. In conclusion, low level of serum sRAGE is a good biomarker for disease other than diabetes and renal disease. A unified formula that takes into consideration of AGEs, sRAGE, and esRAGE such as AGE/sRAGE or AGEs/esRAGE would be better biomarker than sRAGE or esRAGE for all AGE-RAGE-associated diseases including diabetes and renal disease.

Keywords

- ▶ advanced glycation end products
- ▶ soluble receptor for AGEs
- ▶ endogenous secretory receptor for AGEs
- ▶ biomarker
- ▶ coronary artery disease
- ▶ diabetes
- ▶ renal dysfunction
- ▶ unified biomarker for AGE-RAGE-associated diseases

Low levels of soluble receptors for advanced glycation end products (sRAGE) have been suggested to be marker of disease states. However, the levels of sRAGE are elevated in some disease states. The contradictory findings have thrown shadow on the suggested use of low sRAGE as a marker for diseases. In this review, I am going to overview the status of the sRAGE as a marker of the disease processes. In doing so I am going to briefly describe the basics of AGEs and its cell surface receptor (RAGE) and circulating recep-

tors (soluble receptor for AGEs [sRAGE] and endogenous secretory receptor [esRAGE]), the disease states where the levels of AGEs are elevated and the levels of sRAGE and esRAGE are decreased or elevated, and suggest why sRAGE or esRAGE are biomarker for disease states. A better solution for use of sRAGE and esRAGE in combination with AGEs as biomarkers of disease is provided. This will put to rest the controversy of use of sRAGE alone as a marker of disease.

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AGEs–RAGE Axis

AGEs are a heterogeneous group of irreversible adducts resulting from nonenzymatic glycation and oxidation of proteins, nucleic acids, and lipids.^{1–3} AGEs formation proceeds slowly under euglycemic condition but is accelerated in hyperglycemia, oxidative stress, and conditions where protein and lipid turnovers are prolonged.⁴ There are four receptors for AGEs: full length RAGE, N-truncated RAGE, and C-truncated RAGE which has two isoforms, sRAGE and esRAGE. Full length RAGE is a multiligand member of immunoglobulin superfamily cell surface receptor.⁵ Its binding with various ligands results in alteration of several cell function through modulation of intracellular signaling, activation of nuclear-factor kappa-B, gene expression and release of inflammatory cytokines, and elevation of reactive oxygen species (ROS).^{6–8} Interaction of AGEs and RAGE had adverse effects on cell function and initiates and helps in progression of the disease. N-truncated RAGE resides in the plasma membrane, but its function is poorly understood. C-truncated isoforms lack cytosolic and transmembrane domain and circulate in the blood. There are two isoforms of C-truncated RAGE: total soluble RAGE (sRAGE) and esRAGE. sRAGE is formed from the cleavage of the native membrane receptor mediated by disintegrins and MMPs.⁹ esRAGE is formed from alternative splicing of native membrane receptor.¹⁰ Serum levels of sRAGE are five times higher than esRAGE in healthy subjects.¹⁰ Measurement of sRAGE includes esRAGE. Both sRAGE and esRAGE act as a decoy for RAGE ligands by sequestering RAGE ligands or competing with full RAGE for ligand binding¹¹ and thus have cytoprotective effect against AGEs–RAGE interaction.

Conditions Where sRAGE or esRAGE Levels Are Elevated

Serum levels of sRAGE and esRAGE are elevated in type 2 diabetic patients with coronary artery disease or with atherosclerotic burden.^{12,13} Serum levels of sRAGE are high in type 2 diabetes compared with control.¹⁴ However, the serum levels of sRAGE have been reported low in type 2 diabetic patients compared with other controls.¹⁰ Challier et al¹⁵ reported that serum levels of sRAGE are higher in type 1 diabetes compared with nondiabetic control. Higher levels of sRAGE in type 1 diabetic patients are associated with incidental fatal and nonfatal cardiovascular disease.¹⁶ However, esRAGE levels are reduced in type 1 diabetes compared with nondiabetic controls.^{10,15,17} Elevated levels of sRAGE have been reported in patients with impaired renal function especially those with end-stage renal disease.^{18,19} Plasma levels of sRAGE are positively correlated with macro- and microvascular complications and renal dysfunction in type 1 diabetes.²⁰ Elevated levels of sRAGE have been reported in patients with decreased renal function mainly with end-stage renal disease.²¹ These data suggest that serum sRAGE levels are elevated and esRAGE levels are reduced in both type 1 and type 2 diabetes patients. The serum levels of sRAGE are also elevated in patients with impaired renal function and end-stage renal disease.

Conditions Where sRAGE or esRAGE Levels Are Low

Several investigators have reported that serum levels of sRAGE are lower in patients with coronary artery disease and atherosclerotic burden disease in nondiabetic men.^{22–27}

Besides coronary artery disease and atherosclerosis, low levels of sRAGE have also been reported in hypercholesterolemia,²⁸ essential hypertension,²⁹ and Alzheimer disease and vascular dementia.³⁰ sRAGE levels are significantly lower in patients with chronic obstructive pulmonary disease than in age- and sex-matched individual without airway obstruction.^{31,32} esRAGE levels of serum in patients with heart failure decreased in both diabetic and nondiabetic patients.³³ These data suggest that both sRAGE and esRAGE are low in nondiabetic patients.

Alteration in the Circulating Levels of AGEs in Disease State

Serum levels of AGEs are elevated in patients with coronary artery disease.^{26,34,35} The levels of AGEs are 20 to 30% higher in people with uncomplicated type 1 diabetes^{36–38} and 40 to 100% higher in people with type 2 diabetes complicated with coronary artery disease or microalbuminuria.^{39,40} Kilhovd et al⁴⁰ reported that serum levels of AGEs are increased in patients with type 2 diabetes compared with nondiabetic control subjects and that type 2 diabetic patients with coronary heart disease (CHD) had higher serum levels of AGEs compared with CHD patients without type 2 diabetes. The levels of serum AGEs are elevated in diabetic and nondiabetic subjects with coronary artery disease or renal dysfunction.^{41,42} The serum levels of AGEs in diabetic patients with hemodialysis are sixfold higher than those in patients with normoalbuminuria and microalbuminuria.⁴³ The levels of serum AGEs are 5- to 100-fold higher in patients with end-stage renal disease compared with control subjects.^{44–46} These data suggest that circulating levels of AGEs are much higher in patients with diabetes and renal disease. Endogenous AGEs are determined by AGEs formation (hyperglycemia and oxidative stress) and renal excretion of AGEs. The formation and accumulation of AGEs progress at an accelerated rate in diabetes. It has been reported that the serum levels of AGEs in diabetic nephropathy is mainly due to decreased excretion by kidney rather than increased formation.⁴³ Impairment of renal function reduces AGEs clearance in both diabetic and nondiabetic subjects.⁴⁷

Why sRAGE Is Reduced in Some Diseases and Elevated in Others While esRAGE Is Reduced in All Diseases?

sRAGE and esRAGE counteract the effect of AGE and RAGE interaction by binding with AGEs. Both sRAGE and esRAGE neutralize the age-mediated damage by acting as a decoy. Low levels of sRAGE have been proposed as a biomarker of numerous disease states.^{21–32} However, in patients with

diabetes, the sRAGE levels are elevated compared with control subjects.¹²⁻¹⁶ These data suggest that low serum levels of sRAGE may not be considered as a biomarker of all diseases. This raises questions as to why sRAGE levels in serum are elevated and esRAGE reduced in diabetic patients.

Patients with diabetes have higher levels of AGEs and sRAGE compared with controls, and levels of serum AGEs are positively correlated with serum sRAGE. AGEs upregulate RAGE expression in various tissue.^{48,49} There is a close correlation between serum levels of AGEs and endothelial RAGE expression.⁵⁰ AGEs colocalize with RAGE, and AGEs-rich vasculature exhibits increased RAGE immunoreactivity.^{51,52} It is also known that there is a positive correlation between serum AGEs and sRAGE.¹⁴ esRAGE levels in the serum are correlated with AGEs in type 1 diabetes.⁵³ The serum levels of sRAGE are positively correlated with the serum levels of AGEs in diabetic and nondiabetic patients.¹⁴ Also serum levels of sRAGE have been reported to correlate with the levels of AGEs in the vessel wall.⁵⁴ Yamagishi et al⁵⁵ have reported that serum levels of sRAGE are positively associated with serum levels of AGEs in nondiabetic general population and that the sRAGE levels are elevated in parallel with serum esRAGE. sRAGE levels are elevated in type 1 and type 2 diabetes¹²⁻¹⁶ and in renal disease.¹⁹⁻²¹

The possibility exists that the elevated levels of sRAGE in diabetes and renal impairment may be due to a marked increase in the levels of serum AGEs which in turn would increase the expression of RAGE. Since both sRAGE and esRAGE are derived from RAGE, an alteration in the RAGE will be reflected in the alteration in sRAGE and esRAGE. Why then sRAGE is elevated while esRAGE is reduced in diabetes and renal disease? As mentioned earlier, esRAGE is a spliced variant of RAGE and sRAGE is a proteolytically cleaved form mediated by MMPs.^{9,56} The reason for elevated levels of sRAGE could be due to elevated levels of MMPs in diabetes and renal disease. Elevated levels of MMPs would increase the formation of sRAGE. High levels of AGEs in diabetes and renal disease as compared with other disease states would increase the expression of RAGE and hence increased formation of sRAGE. The question arises as to why MMPs will be elevated in diabetes and renal dysfunction?

In this context, it has been reported that AGEs induce expression and production of MMP-9 in macrophages.⁵⁷ Vascular MMP-9 activity is increased in diabetic patients.⁵⁸ AGEs increases expression of MMP-1, -3, -9, and -13 in human osteoarthritic chondrocytes.⁵⁹⁻⁶¹ Uemura et al⁶² reported an increase in vascular MMP-9 in diabetic patients. AGEs induce expression of MMP-2 and -9.⁶³⁻⁶⁵ Expression of MMP-2 and -9 is upregulated in type 2 diabetes.⁶⁶ Since levels of serum AGEs are markedly increased in patients with diabetes and end-stage renal disease, it is expected that the levels of MMPs would increase markedly in these conditions. There is another way of increasing expression of MMPs. Interaction of AGEs with RAGE increases production of ROS.^{4,7-9} ROS is known to increase the expression and activity of MMPs.^{67,68} The increases in expression and activity would increase levels of sRAGE in the serum. In spite of elevated levels of sRAGE, there is diabetic complication. This could be due to the fact that

increase in the serum levels of sRAGE is not sufficient to remove the large amount of serum AGEs effectively.

Suggested Biomarkers for Diseases Associated with AGE-RAGE Axis

From the foregoing section, it appears that sRAGE and esRAGE levels in plasma are reduced or elevated in disease state. Reduced levels of serum sRAGE²²⁻³³ and esRAGE^{10,15,17,69} have been suggested to be biomarkers for diseases. However, it is known that sRAGE and esRAGE are elevated in other diseases. It appears that sRAGE or esRAGE by alone may not be a universal biomarker disease because their serum levels are elevated in some and reduced in others. AGE-RAGE axis involves four players: AGEs, cellular receptor RAGE, circulating receptors sRAGE, and esRAGE. In humans, it is not possible to measure cell receptor RAGE. However, AGEs, sRAGE, and esRAGE can be measured in serum. The other player besides sRAGE and esRAGE should be considered in the equation of universal biomarker for diseases associated with AGE-RAGE system. If only low sRAGE is considered as a disease biomarker, it cannot be applicable to diabetes and renal dysfunction because it is elevated in these diseases. Similarly, if only low serum esRAGE is considered as disease biomarker, then it will not be applicable for diseases where its levels are elevated. The serum levels of sRAGE and esRAGE have to be considered in conjunction with the serum levels of AGEs to identify a suitable universal biomarker for diseases. AGE is an important partner in the formulation of a universal biomarker. Complications occur in diabetes in spite of increased levels of sRAGE. This suggests that the elevation levels of serum AGEs are greater than elevation of sRAGE. Elevated levels of serum sRAGE are not sufficient to handle large amount of AGEs effectively. It will be scientifically sound to use universal equation using both AGEs and circulating RAGE for disease biomarker. Unified formula for biomarker of disease should be AGEs/sRAGE or AGEs/esRAGE. This formula will be better than sRAGE or esRAGE alone as a biomarker for diseases that are associated with AGE-RAGE axis. Since the serum levels of sRAGE are five times higher than esRAGE in healthy subjects, the AGEs/sRAGE may be better biomarker than AGEs/esRAGE.

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