Does AGE–RAGE Stress Play a Role in the Development of Coronary Artery Disease in Obesity?

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Abstract
This article deals with the role of AGE (advanced glycation end products)–RAGE (receptor for AGE) stress (AGE/sRAGE) in the development of coronary artery disease (CAD) in obesity. CAD is due to atherosclerosis in coronary artery. The serum/plasma levels of AGE and sRAGE are reduced, while AGE–RAGE stress and expression of RAGE are elevated in obese individuals. However, the levels of AGE are elevated in obese individuals with more than one metabolic syndrome. The increases in the AGE–RAGE stress would elevate the expression and production of atherogenic factors, including reactive oxygen species, nuclear factor-kappa B, cytokines, intercellular adhesion molecule-1, vascular cell adhesion molecule-1, endothelial leukocyte adhesion molecules, monocyte chemoattractant protein-1, granulocyte-macrophage colony-stimulating factor, and growth factors. Low levels of sRAGE would also increase the atherogenic factors. The increases in the AGE–RAGE stress and decreases in the levels of sRAGE would induce development of atherosclerosis, leading to CAD. The therapeutic regimen for AGE–RAGE stress–induced CAD in obesity would include lowering of AGE intake, prevention of AGE formation, degradation of AGE in vivo, suppression of RAGE expression, blockade of AGE–RAGE interaction, downregulation of sRAGE expression, and use of antioxidants. In conclusion, the data suggest that AGE–RAGE stress is involved in the development of CAD in obesity, and the therapeutic interventions to reduce AGE–RAGE would be helpful in preventing, regressing, and slowing the progression of CAD in obesity.

Keywords
► advanced glycation end products
► receptor for AGE
► soluble receptor for AGE
► atherosclerosis
► atherogenic factors
► AGE–RAGE stress
► obesity
► coronary artery disease

In adult, based on body mass index (BMI), which is the weight (kg)/height (m2), underweight, normal, overweight, and obesity have been classified as follows:1 underweight, <18.5 kg/m2; normal, 18.5 to 24.9 kg/m2; overweight, 25 to 29.9 kg/m2; and obesity, >30 kg/m2. Obesity is further classified into three categories: I, 30 to 34.9 kg/m2; II, 35 to 39.9 kg/m2; and III, ≥40.0 kg/m2, which is extreme obesity. Obesity is a global epidemic.2 Prevalence of obesity has increased over the last few decades in epidemic proportions.3 Prevalence of obesity is 47% in Hispanics, 46.8% in
non-Hispanic blacks, 37.9% in non-Hispanic whites, and 12.7% in Asians. Prevalence of obesity is 36.5% in the western world. Obesity is associated with type 2 diabetes, hypertension, heart disease, sleep apnea, and certain type of cancer. Obese patients have increased preponderance for development of atherosclerotic diseases. Autopsy has shown that atherosclerotic changes in the coronary artery are markedly elevated in patients with multiple risk factors including obesity. Obesity is an independent risk factor for coronary artery disease (CAD). It has been reported that loss of weight has favorable effects on the development of CAD. It has been reported that 43 and 24% of all coronary revascularization in recent years were performed in overweight and obese patients, respectively. These data suggest that CAD is associated with obesity. The mechanisms involved in the development of atherosclerosis in obesity have been suggested to be abnormality in lipid metabolism, insulin resistance, inflammation, endothelial dysfunction, and adipokine imbalance.

### AGE–RAGE Axis and AGE–RAGE Stress

AGEs are heterogeneous groups of irreversible adducts produced by nonenzymatic glycation of glycoxidation of proteins, lipids, and nucleic acid with reducing sugars. There are mainly three receptors for AGEs, including full-length receptor for AGEs (RAGE), which is cell-bound and is multiligand, N-truncated RAGE, and c-truncated RAGE. The function of N-truncated RAGE is not known. The c-truncated RAGE circulates in the blood and other body fluids and lacks transmembrane and cytoplasmic domain. C-truncated RAGE has two isoforms, cleaved RAGE (cRAGE) and endogenous secretory RAGE (esRAGE). c-RAGE is generated at the cell surface by proteolytic cleavage of full-length RAGE at the boundary between its extracellular and transmembrane part. Matrix metalloproteinase-9 (MMP-9) and ADAM metallopeptidase domain 10 (ADAM10) are involved in cleavage. esRAGE is formed from alternative splicing of RAGEpre-mRNA. Total sRAGE comprises both cRAGE and esRAGE. Both sRAGE and esRAGE are measured by enzyme-linked immunosorbent assay (ELISA) kit. cRAGE is the difference between sRAGE and esRAGE. Serum levels of esRAGE are 20 to 30% of the serum levels of sRAGE.

### Atherogenic Function of AGE

AGE can induce atherosclerosis by affecting the factors involved in the development of atherosclerosis. It makes low-density lipoprotein (LDL) more atherogenic by modifying apoB100. AGE glycates apoB100 and phospholipid component of LDL, which affects the LDL clearance and enhances the susceptibility of LDL oxidation. Oxidized LDL reduces its recognition by scavenger receptor in the liver and hence levels of oxidized LDL in the body are increased. Glycated LDL increases smooth muscle cell proliferation and differentiation. Reverse cholesterol transport is interfered by AGE and that increases the extracellular accumulation of cholesterol. AGE increases the accumulation of cholesterol and cholesterol esters in macrophages in vitro. AGE enhances the synthesis of extracellular matrix, traps endothelial LDL, and cross-binds with collagen. Matrix-bound AGE enhances the synthesis of endothelin, which is implicated in the development of atherosclerosis.

### Atherogenic Function of Interaction of AGE with RAGE

Interaction of AGE with RAGE generates reactive oxygen species (ROS) through activation of nicotinamide adenine dinucleotide phosphate hydrogen (NADPH) oxidase. ROS activates nuclear factor-kappa B (NF-κB), which in turn activates varieties of proinflammatory cytokine genes, including tumor necrosis factor-α (TNF-α), TNF-β, interleukin (IL)-1, IL-2, IL-6, IL-8, and interferon gamma. AGE–RAGE interaction increases the expression of intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and E-selectin through NF-κB. Expressions of ICAM-1, VCAM-1, and endothelial leucocyte adhesion molecules are also upregulated by ROS. AGE–RAGE interaction upregulates the expression of monocyte chemotactic protein-1 (MCP-1) mRNA in mesangial cells, and MCP-1 and vascular endothelial growth factor in human cultured mesangial cells. AGE–RAGE interaction upregulates the expression and secretion of granulocyte-macrophage colony-stimulating factor (GM-CSF) and the expression of insulin-like growth factor-1 and platelet-derived growth factor. AGE–RAGE interaction enhances the expression of transforming growth factor-β (TGF-β), which takes part in the formation of extracellular matrix. AGE–RAGE interaction in smooth muscle cells increases chemotactic migration, cell proliferation, and production of fibrogen. Cytokines, adhesion molecules, GM-CSF, and growth factors are required in the development of atherosclerosis.
Antiatherogenic Function of sRAGE and esRAGE

sRAGE acts as a protective endogenous decoy for RAGE by binding with AGE or other RAGE ligands.\(^{64,65}\) Binding of sRAGE or esRAGE with AGE does not activate intracellular signaling.\(^{66}\) sRAGE is a competitive inhibitor of interaction of AGE with RAGE.\(^{67}\) Interaction of sRAGE with AGE would reduce the amount of AGE to interact with RAGE and hence the atherogenic factors such as ROS, NF-κB, MCP-1, GM-CSF, cytokines, cell adhesion molecules, and growth factors will be reduced, resulting in the protection of atherosclerosis.

AGE–RAGE Stress

Prasad and Mishra\(^{68}\) have coined three terminologies (stressors, antistressors, and AGE–RAGE stress) for AGE–RAGE axis. AGE and RAGE have been coined as stressors. Enzymatic degradation of AGE (glyoxalase-1 and glyoxalase-2), receptor-mediated degradation of AGE (AGE receptor [AGER]-1, AGER-2, and AGER-3), and sRAGE have been coined as antistressors. AGE–RAGE stress has been coined as a shift in the balance between stressors and antistressors in favor of stressors. Prasad and Mishra\(^{68}\) have developed formulas for assessment of AGE–RAGE stress and have suggested that the ratio of AGE/sRAGE formula would be a simple and feasible measure of AGE–RAGE stress. A high ratio of AGE/sRAGE indicates the presence of AGE–RAGE stress, resulting in tissue damage, initiation, and progression of the diseases and their complications.

Serum/Plasma and Tissue Levels of AGE in Obesity

Serum/plasma levels of AGEs have been reported to be variable in obese individuals. Serum levels of AGE are elevated in obese individuals with more than one metabolic syndrome.\(^{69}\) Measurements of serum levels of AGE were made in diabetic obese, diabetic nonobese, nondiabetic obese, and nondiabetic nonobese individuals by Amin et al.\(^{70}\) They observed that the levels of carboxymethyl-lysine (CML) were markedly elevated in diabetic obese, diabetic nonobese, and nondiabetic obese compared with nondiabetic nonobese individuals. Also, the serum levels of CML were significantly elevated in diabetic obese compared with diabetic nonobese individuals. The CML levels were significantly elevated in nondiabetic obese compared with nondiabetic nonobese individuals. They observed that CML levels were predictor for obesity based on regression analysis. They also reported that there was a positive correlation between the levels of CML and BMI in all four groups.

There are reports showing a decrease in the serum levels of AGE in obesity. Children/adolescents with obesity had significantly lower levels of plasma CML and fluorescent AGE as compared with nonobese controls.\(^{71}\) Plasma levels of CML have been reported to be lower among obese middle school children.\(^{72}\) Gaens et al\(^{73}\) reported a lower levels of plasma CML in obese individuals compared with lean adults. Serum AGE (CML and pentosidine) levels were significantly lower in individuals with higher BMI.\(^{74}\) They also reported that there was a negative correlation of CML and pentosidine with BMI. However, Kilhovd et al\(^{75}\) have reported that there was no significant correlation between AGE and BMI. It has been reported that the serum levels of CML were lower in obese adolescents (15–19 years) than in adolescents with normal body weight.\(^{76}\) The authors also reported that the levels of total AGE measured by fluorescence were lower in obese adolescents compared with adolescents with normal body weight.

Obesity has been reported to be associated with increased accumulation of CML and expression of RAGE in omental adipose tissue and with decreased levels of plasma AGE as compared with lean individuals.\(^{77}\) RAGE ligands are elevated in metabolic organs of wild-type mice on high-fat diet.\(^{78}\) These investigators\(^{78}\) also reported that sRAGE administration significantly reduced weight gain in mice on high-fat diet. The formation of CML in adipose tissue is elevated in obesity.\(^{79,80}\) Although the tissue levels of AGE are elevated in obesity, the serum levels of AGE are reduced.\(^{71}\) There is an inverse association between serum CML and fat mass.\(^{81}\)

The serum levels of CML in metabolically healthy adolescents were similar to normal weight adolescents.\(^{82}\) AGE-related fluorescence in plasma is not significantly affected by feeding fat that increases body weight.\(^{83}\) It has been reported that the serum levels of AGE were reduced by 7.21% with low calorie diet for 2 months in overweight individuals, and this change in AGE was positively correlated with change in BMI.\(^{84}\)

In summary, the data show that the levels of serum/plasma AGE are reduced in obese individuals, while the serum levels of AGE are elevated in obese individuals with more than one metabolic syndrome. Also, obesity is associated with increased accumulation of CML in omental adipose tissue and metabolic organs of wild-type mice on high-fat diet.

Expression of RAGE in Obesity

Obesity has been reported to be associated with increased expression of RAGE in omental adipose tissue compared with lean individuals.\(^{77}\) There is an elevation of RAGE expression in adipose tissue of obese individuals and has been reported to play a role in atherosclerosis.\(^{85}\) However, Leuner et al\(^{86}\) have shown that absence of RAGE accelerates weight gain in mice. Blockade of RAGE with sRAGE in wild mice suppressed weight gain.\(^{78}\) RAGE expression in mononuclear cells of peripheral blood of obese persons were similar to that in control persons.\(^{87}\)

In summary, AGE expression in adipose tissue is upregulated, while its expression in mononuclear cells of blood remained unaltered in obese individuals.

Serum/Plasma Levels of sRAGE in Obesity

Serum levels of sRAGE were lower in small and large obese children compared with normal-weighing children at
birth. The levels of serum sRAGE were lower in obese adolescent individuals compared with adolescent with normal weight. sRAGE levels were lower in obese prepubertal children compared with normal-weight children. He et al reported that BMI is an independent predictor of plasma sRAGE levels in adolescents. However, Rowisha et al reported a decrease in the levels of serum sRAGE in obese adolescents. Serum levels of sRAGE were lower in obese diabetics, nonobese diabetics, and nondiabetic obese compared with nondiabetic nonobese individuals. Amin et al reported that regression analysis of the sRAGE shows that sRAGE is a predictor of obesity. These investigators also showed that sRAGE was negatively correlated with CML and BMI. sRAGE is reduced in individuals with obesity. Guclu et al reported a significant negative correlation of sRAGE with body weight, BMI, and waist and hip circumference. Obese women have lower sRAGE levels compared with women with normal weight, and there was an inverse correlation of sRAGE with BMI and total body fat. D’Adamo et al have shown that sRAGE and esRAGE levels in serum were significantly lower in obese prepubertal children with or without liver steatosis. Brix et al reported a significant increase in total sRAGE as a result of weight loss following bariatric surgery. This also shows that levels of sRAGE are reduced in obesity. In summary, serum/plasma levels of sRAGE and esRAGE are lower in obese individual compared with nonobese individuals. Also, there is an inverse correlation between sRAGE and AGE.

Serum/Plasma Levels of esRAGE in Obesity

Chiavaroli et al have reported that serum levels of esRAGE were lower in small born weight and large born weight obese children than normal weight of similar age group. Miranda et al have shown that loss of weight and body fat mass is associated with increases in the serum levels of sRAGE, esRAGE, and cRAGE. Levels of esRAGE in plasma are associated with obesity in women.

In summary serum/plasma levels of esRAGE are lower in obese individuals as compared with nonobese individuals.

AGE–RAGE Stress in Obesity

No data are available in the literature regarding AGE–RAGE stress in obesity. All other investigators have measured either AGE or sRAGE in obesity, except Amin et al who measured both AGE and sRAGE in the same group of patients. However, they did not assess AGE–RAGE stress. Amin et al have measured AGE and sRAGE in diabetic obese, diabetic nonobese, nondiabetic obese, and nondiabetic nonobese patients. We calculated the AGE–RAGE stress using their data. We observed that AGE–RAGE stress in diabetic obese, diabetic nonobese, nondiabetic obese, and nondiabetic nonobese (healthy control) were, respectively, 154.06, 109.1, 67.3, and 31.1. The data show that AGE–RAGE stress is 2.16 times higher in obese nondiabetic, 3.5 times higher in diabetic nonobese, and 4.95 times higher in diabetic obese individuals compared with nondiabetic nonobese controls. The data suggest that AGE–RAGE stress is 1.6 times higher in patients with nonobese diabetes compared with nondiabetic obese patients. The data also suggest that obese patients with diabetes have the highest AGE–RAGE stress as compared with controls, obese, and diabetic patients. In conclusion, the AGE–RAGE stress is markedly elevated in obese patients compared with the controls.

Mechanism of AGE–RAGE Axis–Induced Coronary Artery Disease in Obesity

In the previous section, we have described the atherogenic effects of AGE, interaction of AGE with RAGE, and antiatherogenic effects of sRAGE. Increases in the serum levels of AGE and expression of RAGE would produce atherosclerosis in the coronary artery, resulting in CAD. However, the serum levels of AGE are reduced in obesity and hence the chances of development of atherosclerosis in the coronary artery of obese individuals would be reduced. However, this does not happen in obesity. Atherosclerosis develops in obesity. Expression of RAGE is elevated in adipose tissue of obese individuals, which would increase the chances of development of atherosclerosis. However, RAGE expression in mononuclear cells of peripheral blood of obese individuals has been reported to be unaltered. As described earlier in the section “Serum/Plasma Levels of sRAGE in Obesity,” the levels of sRAGE and esRAGE are reduced in obesity, which would increase the chances of development of atherosclerosis. Decreases in the serum levels of AGE should have protected the development of atherosclerosis and CAD in obese individuals. However, this does not happen in obesity. Obesity is an independent risk factor for CAD. Why does this discrepancy exist? Prasad has reported that sRAGE does not serve as a universal risk marker of disease. AGE–RAGE axis comprises AGE, RAGE, and sRAGE. Hence, sRAGE alone cannot serve as risk marker of the disease. As described earlier in the section “AGE–RAGE Stress,” AGE–RAGE stress, which is the ratio of AGE/sRAGE, indicates tissue damage, initiation and progression of disease, and its complications. The limited data show that AGE/sRAGE is elevated in obese individuals. Although the serum levels of AGE and sRAGE are reduced in obese individuals, the ratio of AGE/sRAGE is elevated. The increase in the ratio of AGE/sRAGE suggests that the levels of AGE are greater than the levels of sRAGE in obese individuals as compared with those in nonobese individuals. As described earlier, increased levels of AGE and RAGE are atherogenic. Antiatherogenic effects of sRAGE, described in the section “Antiatherogenic Function of sRAGE and esRAGE,” will be reduced with low serum/plasma levels of sRAGE in obesity. Increased levels of AGE–RAGE stress (AGE/sRAGE) and expression of RAGE, and reduced levels of serum/plasma sRAGE in obese individuals would produce atherosclerosis in coronary artery, leading to CAD. Atherogenic effects of interaction of AGE–RAGE stress with RAGE and reduced levels of sRAGE are depicted in Fig. 1. Interaction of increased AGE–RAGE stress with upregulated RAGE
expression would generate ROS, activate NF-κB, and increase the expression and levels of MCP-1, GM-CSF, cell adhesion molecules, cytokines, and growth factors, leading to the development of coronary artery atherosclerosis. Reduced levels of sRAGE will combine with less amount of AGE and more AGE will be available to interact with RAGE to produce ROS, NF-κB, MCP-1, GM-CSF, cell adhesion molecules, endothelial leukocyte adhesion molecules, cytokines, and growth factors to initiate and maintain the development of coronary atherosclerosis, leading to CAD. The role of these biomolecules in the formation of atherosclerosis is not being described here. The details of the roles of these biomolecules in the development of atherosclerosis have been reported earlier by Prasad,102 Prasad and Tiwari,64 and Prasad and Bhanumathy.103

ROS generated by interaction of AGE with RAGE can also produce atherosclerosis because ROS has been implicated in the development of atherosclerosis.104,105

**Treatment Strategy for Obesity–Induced Coronary Artery Disease**

The treatment strategy for obesity-induced CAD includes lowering of AGE levels in the body, degradation of AGE in vivo, prevention of AGE formation, downregulation of RAGE expression, use of blockers of interaction of AGE with RAGE, upregulation of AGE expression, exogenous administration of sRAGE, and use of antioxidants. These treatment strategies have been described in detail elsewhere by Prasad,15 Prasad and Tiwari,64 and Prasad and Bhanumathy.103

**Perspectives**

The available data on AGE–RAGE axis suggest that AGE–RAGE stress may be involved in the development of obesity-induced CAD. However, there are other risk factors, including abnormality in lipid metabolism, insulin resistance, inflammation, endothelial dysfunction, and adipokines imbalance, which have been implicated in the obesity-induced CAD.13

Adipose tissue comprises two types of fat: white fat (subcutaneous and visceral) and brown fat. White adipocytes preferentially produce good anti-inflammatory adipokines (IL-1, IL-4, IL-10, IL-13) receptor antagonist and TGF under healthy condition.106 White adipocytes in obesity, however, produce bad adipokines (TNF-α, IL-6 angiotensin-II, and leptin).106 These bad adipokines induce development of atherosclerosis.107 C-reactive protein levels are elevated in obesity,108 which would also induce atherosclerosis.109,110

As described earlier in the section “Serum/Plasma and Tissue Levels of AGE in Obesity,” the serum levels of sRAGE are reduced, while the levels of AGE are elevated in adipose tissue.71,81 The significance of this inverse association of AGE and sRAGE is presently unexplainable.

The treatment strategies for AGE–RAGE stress in obesity-induced CAD are reasonable. However, this treatment strategy may not be fully effective because there are other risk factors.
factors besides AGE–RAGE stress that are involved in the development of obesity-induced CAD. This treatment strategy would supplement the other treatment protocol for obesity-induced CAD.

**Conclusion**

Serum/plasma levels of AGE and sRAGE are reduced, while AGE–RAGE stress (AGE/sRAGE) levels are elevated in obese patients. Increased levels of AGE–RAGE stress would induce development of atherosclerosis in coronary artery, leading to CAD through increased production of numerous atherogenic factors. Treatment strategy for AGE–RAGE-induced CAD should be directed toward reduction in intake of AGE, prevention of AGE formation, degradation of AGE in vivo, downregulation of RAGE expression, blockade of binding of AGE with RAGE, upregulation of expression of sRAGE, and use of antioxidants.

**Disclosure**

None.

**Conflict of Interest**

None declared.

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