

# AGE–RAGE Stress and Coronary Artery Disease

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## Abstract

### Keywords

- ▶ advanced glycation end products (AGE)
- ▶ cell receptor for AGE
- ▶ soluble receptors AGE
- ▶ coronary artery disease (CAD)
- ▶ atherosclerosis
- ▶ atherosclerotic plaque rupture
- ▶ AGE–RAGE stress
- ▶ treatment modalities for AGE–RAGE stress-induced CAD

Coronary artery atherosclerosis and atherosclerotic plaque rupture cause coronary artery disease (CAD). Advanced glycation end products (AGE) and its cell receptor RAGE, and soluble receptor (sRAGE) and endogenous secretory RAGE (esRAGE) may be involved in the development of atherosclerosis. AGE and its interaction with RAGE are atherogenic, while sRAGE and esRAGE have antiatherogenic effects. AGE–RAGE stress is a ratio of AGE/sRAGE. A high AGE–RAGE stress results in development and progression of CAD and vice-versa. AGE levels in serum and skin, AGE/sRAGE in patients with CAD, and expression of RAGE in animal model of atherosclerosis were higher, while serum levels of esRAGE were lower in patients with CAD compared with controls. Serum levels of sRAGE in CAD patients were contradictory, increased or decreased. This contradictory data may be due to type of patients used, because the sRAGE levels are elevated in diabetics and end-stage renal disease. AGE/sRAGE ratio is elevated in patients with reduced or elevated levels of serum sRAGE. It is to stress that AGE, RAGE, sRAGE, or esRAGE individually cannot serve as universal biomarker. AGE and sRAGE should be measured simultaneously to assess the AGE–RAGE stress. The treatment of CAD should be targeted at reduction in AGE levels, prevention of AGE formation, degradation of AGE in vivo, suppression of RAGE expression, blockade of RAGE, elevation of sRAGE, and use of antioxidants. In conclusion, AGE–RAGE stress would initiate the development and progression of atherosclerosis. Treatment modalities would prevent, regress, and slow the progression of CAD.

Coronary artery disease (CAD), also known as coronary heart disease (CHD), and ischemic heart disease are due to reduced blood supply to the heart. Coronary artery stenosis manifests in clinical syndrome called stable angina and acute coronary syndrome (ACS). Acute coronary syndrome includes unstable angina and ACS (ST-segment elevated myocardial infarction [STEMI], and non-ST-segment elevated myocardial infarction [NSTEMI]).<sup>1</sup> Although ACS, CHD, and CAD are used interchangeably, they are not the same. ACS is the subcategory of CAD, while CHD is the result of CAD. According to World Health Organization, CAD is the main cause of death globally (>9 million death in 2016).<sup>2</sup> Russia, United States, Ukraine, Germany, and Brazil had the most number of death due to CAD in 2015.<sup>3</sup> They also reported that mortality has progres-

sively decreased from 2005 to 2015. Fifty percent of all death from cardiovascular disease (CVD) is due to CAD.<sup>4</sup> CAD is due to atherosclerosis. As atherosclerosis progresses, atherosclerotic plaques rupture resulting in arterial occlusion or dislodged material from plaques blocking the smaller branches of coronary artery. The risk factors for atherosclerosis or CAD include dyslipidemia,<sup>5,6</sup> diabetes,<sup>7</sup> hypertension,<sup>8</sup> cigarette smoking,<sup>9,10</sup> obesity,<sup>10</sup> hyperhomocysteinemia,<sup>11</sup> and C-reactive protein.<sup>12</sup> Advanced glycation end products (AGE) and its cell receptors RAGE (receptor for AGE), and soluble receptors sRAGE (soluble receptor for AGE) and esRAGE (endogenous secretory receptor for AGE) have been implicated in various diseases including, NSTEMI,<sup>13</sup> restenosis following percutaneous coronary intervention (PCI),<sup>14</sup>

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carotid artery de-endothelialization-induced neointima expansion in wild-type mice,<sup>15,16</sup> streptozotocin-induced diabetes accelerated atherosclerosis in apo-E-deficient mice,<sup>17</sup> and accelerated atherosclerosis in apoE-deficient mice.<sup>18</sup> This chapter addresses the RAGE stress and the role of AGE-RAGE stress in the pathogenesis of atherosclerosis, AGE, RAGE, and sRAGE levels in patients with CAD and the treatment strategy for prevention, regression, and slowing of the progression of CAD.

## AGE-RAGE Stress

AGEs are heterogeneous groups of irreversible adducts produced by nonenzymatic glycation and glycoxidation of proteins, nucleic acid with reducing sugars.<sup>19,20</sup> There are four receptors for AGE: full length cell receptor for AGE (RAGE), N-truncated RAGE, and two C-truncated RAGE. Interaction of AGE with RAGE has adverse effects on cell function and initiates and accelerates the progression of various diseases. This will be discussed in detail in a section on atherogenic effects of AGE and its interaction with RAGE. N-truncated RAGE is bound in the plasma membrane, but its function is not well understood as yet. C-truncated RAGE has two isoforms, cleaved RAGE (c-RAGE), and endogenous secretory RAGE (esRAGE). c-RAGE is proteolytically cleaved from full length RAGE,<sup>21</sup> while esRAGE is produced from alternative mRNA splicing of full-length RAGE.<sup>22</sup> c-RAGE and esRAGE lack cytosolic and transmembrane domain and circulate in the blood. sRAGE comprises of both c-RAGE and esRAGE. Twenty to thirty percent of sRAGE is esRAGE.<sup>23,24</sup> sRAGE binding with ligands does not activate intracellular signaling. Both sRAGE and esRAGE compete with RAGE for ligand binding and thus have protective effects against adverse effects of AGE-RAGE binding. Prasad and Mishra<sup>25</sup> have coined three terminologies in the AGE-RAGE axis that comprises of AGE, RAGE, and sRAGE. AGE and its interaction with RAGE have been coined as stressors because they produce adverse effects. The agents that reduce the adverse effects of AGE and its interaction with RAGE have been coined as antistressors that include endogenous, exogenous, and down regulation of RAGE expression. Endogenous antistressors include enzymatic degraders of AGE (glyoxalase-1, glyoxalase-2), AGE receptor-mediated degraders of AGE (AGE receptor-1 [AGER-1], AGER-2), and sRAGE. Exogenous antistressors include reduction in AGE consumption and exogenous administration of sRAGE. AGE-RAGE stress has been defined as a shift in balance between stressors and antistressors in favor of stressors.<sup>25</sup> Prasad and Mishra<sup>25</sup> have constructed a formula to assess AGE-RAGE stress. The ratio of AGE/sRAGE has been proposed as a simple and feasible measure of AGE-RAGE stress in clinical practice. A high index of AGE-RAGE stress would initiate the development and progression of diseases including CAD.

## Atherogenic Effects of AGE-RAGE Stress

AGE-RAGE stress could produce atherosclerosis in two ways: direct effect of AGE and interaction of AGE with RAGE.

## Direct Effects of AGE

AGE modifies apoB100 that makes low-density lipoprotein (LDL) more atherogenic.<sup>26</sup> Glycation of apoB and phospholipid component of LDL alters the LDL clearance and increases the susceptibility of LDL oxidation.<sup>27,28</sup> Glycated LDL decreases its recognition by LDL receptors,<sup>29</sup> and increases smooth muscle cell proliferation and differentiation.<sup>30,31</sup> AGE interferes with reverse cholesterol transport<sup>29</sup> resulting in extracellular accumulation of cholesterol. AGE enhances accumulation of cholesterol and its esters in macrophages in vitro.<sup>32</sup> AGE increases synthesis of extracellular matrix<sup>33</sup> and cross-binds with collagen.<sup>34</sup> Cross-linking of AGE with collagen and elastin enhances arterial stiffness.<sup>35</sup> Matrix-bound AGE increases expression of endothelin-1<sup>36</sup> that has been suggested to be involved in the development of atherosclerosis.<sup>33</sup> Generation of nitric oxide (NO) is reduced by AGE<sup>37</sup> and oxidized LDL.<sup>38</sup> AGE quenches NO<sup>39</sup> and matrix-bound AGE quenches and inactivates NO.<sup>40</sup> Matrix-bound AGE inhibits antiproliferative activity of NO.<sup>41</sup> In summary, the above data suggest that AGE initiates and helps in progression of atherosclerosis through LDL oxidation, interfering reverse cholesterol transport, altering LDL clearance, increasing smooth muscle cell proliferation and differentiation, increasing expression of endothelin and extracellular matrix, reducing generation of NO, and quenching and inactivation of NO.

## Effects of Interaction of AGE with RAGE

AGE interacts with RAGE to produce reactive oxygen species (ROS)<sup>42</sup> that activates nuclear factor kappa-B (NF- $\kappa$ B) that in turn activates numerous proinflammatory genes of cytokines such as tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin (IL)-1, IL-2, IL-6, IL-8, IL-9.<sup>43,44</sup> Interaction of AGE with RAGE increases expression of intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and E-selectin.<sup>45</sup> ROS itself upregulates the expression of ICAM-1, VCAM-1, and endothelial leucocytes adhesion molecules.<sup>46-48</sup> AGE increases expression of monocyte chemoattractant protein-1 (MCP-1) in mesangial cells,<sup>49</sup> and MCP-1 and vascular endothelial growth factor in human-cultured mesangial cells.<sup>50</sup> Expression and secretion of granulocyte macrophage-colony stimulating factor (GM-CSF) by macrophages is enhanced with AGE.<sup>51</sup> AGE-RAGE interaction enhances expression of insulin-like growth factor-1 and platelet-derived growth factor (PDGF).<sup>52</sup> AGE enhances the expression of transforming growth factor- $\beta$ .<sup>53</sup> These data suggest that AGE-RAGE interaction enhances the expression of biomolecules required for initiation and progression of atherosclerosis. It also implies that sRAGE is protective against AGE-RAGE-induced atherosclerosis.

## Mechanisms Involved in AGE-RAGE Stress-Induced Atherosclerosis and Plaque Rupture

AGE and its interaction with RAGE-induced atherogenic biomolecules have been implicated in atherosclerosis and have been described in detail by Prasad<sup>9</sup> and Prasad and

Bhanumathy.<sup>54</sup> Most of the ACS is associated with plaque rupture.<sup>55,56</sup> Matrix metalloproteinases (MMPs) have been implicated in plaque rupture. There is overexpression of MMPs in atherosclerotic lesions. An increased expression of MMP1 in several cell types in human carotid atherosclerotic plaques and its correlation with histopathological evidence of plaque instability have been reported by Nikkari et al.<sup>57</sup> MMP-9 has been reported to be elevated in atherectomy specimen from patients with unstable angina.<sup>58</sup> IL-1, PDGF, and TNF- $\alpha$  have been shown to stimulate expression of MMPs.<sup>59-61</sup> Oxidative stress increases the expression of MMP-1 and MMP-3.<sup>62,63</sup> ROS may be involved in stability of atherosclerotic plaques.<sup>64</sup> The above data also suggest that AGE and its interaction with RAGE may be involved in the instability and rupture of atherosclerotic plaque and ACS.

### **Serum Levels of AGE, RAGE, sRAGE, esRAGE, and AGE-RAGE Stress in Patients with CAD**

If AGE-RAGE stress is involved in the pathophysiology of CAD, then the serum levels of AGE, RAGE, and AGE/sRAGE should be elevated while the levels of sRAGE and esRAGE would be reduced. The following section would deal with the serum levels of AGE, RAGE, sRAGE, esRAGE, and AGE/sRAGE in patients with CAD.

### **Serum Levels of AGE in Patients with CAD**

Levels of AGEs have been measured in serum/plasma and skin autofluorescence in patients with CAD. Skin autofluorescence is a noninvasive measurement of levels of AGE in skin.<sup>65</sup> Serum levels of AGE are elevated in CAD patients with type 2 diabetes as compared with CAD patients without diabetes.<sup>66</sup> Kilhovd et al<sup>67</sup> measured the serum levels of AGEs in 1141 nondiabetic individuals at base line and followed up for 18 years. Eighty-four patients died of CAD during this follow-up period and the death was associated with elevated levels of serum AGE. The data suggest that serum levels of AGE can predict CHD mortality in nondiabetic women but not in nondiabetic men. Kanauchi et al<sup>68</sup> measured serum levels of AGE in nondiabetic patients with significantly stenosed vessels assessed by coronary angiography, and found that serum levels of AGEs were significantly higher in nondiabetic subjects with CAD than in control subjects and were significantly correlated with number of significantly stenosed vessels. The levels of AGEs were significantly higher in group with three vessels disease than in group with zero and 1 vessel disease. McNair et al<sup>13</sup> have reported that the serum levels of AGE were higher in NSTEMI subjects compared with control subjects. The also showed that the levels AGE were higher to similar extent in patients with 1 vessel, 2 vessels, and 3 vessels disease compared with control subjects. McNair et al<sup>14</sup> reported that the serum levels of AGE pre-PCI were higher in patients of both groups who developed or did not develop post-PCI restenosis but the post-PCI levels of AGE were significantly higher in patients who developed post-PCI restenosis compared with control subjects. Serum AGE levels are elevated in

patients undergoing PCI and is reported to be an independent risk factor for restenosis in diabetic patients.<sup>69</sup> Serum levels of AGE were elevated in type 2 diabetic patients with obstructive CAD compared with diabetics with nonobstructive CAD and levels of AGE correlated with degree of coronary artery atherosclerosis.<sup>70</sup> This association was independent of other risk factors for CAD including hypertension, cigarette smoking, hyperlipidemia, and hyperuricemia. Serum levels of AGE have been suggested to be a biomarker for severity of coronary artery atherosclerosis in type 2 diabetic patients independent of hypertension, hyperlipidemia, and cigarette smoking.<sup>71</sup> Kerkeni et al<sup>72</sup> have reported that there was an association between elevated levels of pentosidine (a type of AGE) and obstructive CAD and its severity was independent of diabetes. Plasma levels of AGEs like carboxymethyl-lysine (CML), carboxyethyl-lysine (CEL), pentosidine, and tetrahydropyrimidine (THP) were elevated in diabetic patients.<sup>73</sup> Higher levels of plasma pentosidine but not CML, CEL, and THP were associated with moderate-to-high coronary artery calcium score compared with a low coronary artery calcium score in type 1 diabetic patients. An association between higher CML and cardiovascular mortality has been reported in a prospective study of over 1,000 patients over 65 years of age and followed for a median time of 6 years.<sup>74</sup> Lu et al<sup>75</sup> in a cross-section study showed that the serum levels of glycated albumin were significantly elevated in patients with both type 2 diabetes and significant CAD. They also reported that there was no significant difference in glycated albumin levels in nondiabetic patients with or without CAD. Glycated albumin levels were associated with angiographic CAD severity, extent and number of diseased coronary arteries in diabetic CAD patients. Serum levels of AGE were significantly elevated in diabetic patients with CHD as compared with those without CHD.<sup>76</sup>

In some studies, AGE levels were measured with skin autofluorescence and the results were similar to that measured with immunoassay in CAD patients. Mulder et al<sup>77</sup> reported that skin autofluorescence is elevated in patients with stable CAD compared with healthy control. Yozgatli et al<sup>78</sup> have shown that there was a correlation between increased levels of skin autofluorescence and CAD independent of hemoglobin A1c levels in type 2 diabetic patients. Conway et al<sup>79</sup> elevated skin autofluorescence was associated with severity of coronary artery calcium score in type 1 diabetics. There was no significant difference in skin autofluorescence among unstable angina, NSTEMI, and STEMI at admission. However, AGE levels increased significantly in patients with cardiac events during follow-up.<sup>80</sup> It has been reported that increased levels of AGE in patients with diabetes accelerate the development and progression of heart failure both indirectly through coronary dysfunction and atherosclerosis,<sup>81</sup> and directly through its action on myocardium.<sup>82</sup> In summary, the serum levels of AGE are elevated in patients with CAD.

### **Serum Levels of sRAGE in CAD Patients**

There are conflicting reports about the use of sRAGE as a biomarker for CVD. Selvin et al<sup>83</sup> measured the plasma levels

of sRAGE in 1201 participants who had normal kidney function, and no history of CVD, and followed up for 18 years. They found that during that period 192 (16%) participants developed CAD events that was associated with low levels of plasma sRAGE suggesting that low sRAGE levels were biomarker of future chronic CAD. Falcone et al<sup>84</sup> measured the plasma levels of sRAGE in 328 nondiabetic patients with angiographically proven CAD and 328 age-matched healthy control and showed that low plasma levels of sRAGE were independently associated with CAD in nondiabetic individuals. It has been reported that plasma levels of sRAGE were significantly lower in patients with ACS (unstable angina and myocardial infarction) than in patients with stable angina.<sup>85</sup> They also reported that the plasma levels of sRAGE were not affected by statin therapy, number of diseased vessels, and extent of coronary disease. Other investigators<sup>84-87</sup> have also reported reduced plasma levels of sRAGE in patients with ACS and stable angina when compared with control subjects. It has been reported that plasma levels of sRAGE were significantly lower in patients with CAD with or without peripheral vascular disease (PVD) compared with control.<sup>88</sup> They also showed that CAD patients with PVD had lower plasma sRAGE compared with those without PVD. Low levels of serum sRAGE in patients with suspected CAD were predictive of cardiovascular events after follow-up for 48 months.<sup>89</sup> Low levels of sRAGE have been reported to be associated with high coronary calcium score.<sup>90</sup> Serum levels of sRAGE have been reported to be lower in NSTEMI patients compared with control subjects.<sup>13</sup> Pre-PCI levels of serum sRAGE were significantly lower in NSTEMI patients who developed or not developed post-PCI restenosis compared with control subjects; however, the levels of sRAGE were significantly lower in patients who developed restenosis compared with those who did not develop restenosis.<sup>14</sup> Pre- and post-PCI levels of sRAGE in NSTEMI patients were similar who did not develop restenosis following PCI. On the other hand, post-PCI levels of sRAGE were significantly lower than those who developed restenosis.<sup>14</sup> McNair et al<sup>13</sup> have shown that sRAGE levels were inversely associated with number of stenosed vessels. McNair et al<sup>91</sup> also reported that levels of sRAGE were lower in NSTEMI patients compared with control and that there was a negative correlation between sRAGE and cardiac troponin-I (cTnI).

However, there are numerous papers showing increases in the serum levels of sRAGE in patients with CAD. It has been reported that plasma levels of sRAGE were higher in patients with NSTEMI-ACS than in patients with stable angina and positively correlated with cTnI.<sup>92</sup> Nakamura et al<sup>93</sup> have shown that serum levels of sRAGE were significantly higher in diabetic patients with CAD than in diabetic patients without CAD. sRAGE levels are directly correlated with presence and severity of CAD in patients with and without diabetes.<sup>70,94-96</sup> Wang et al<sup>97</sup> measured the plasma levels of sRAGE in patients with normal coronary artery, nonobstructive coronary artery (< 50% stenosed coronary artery), stable angina and ACS, and observed that plasma levels of sRAGE were higher compared with control group, nonobstructive coronary artery, and stable angina group. The

levels did not change significantly in patients with stable angina and nonstenosed coronary artery compared with control subjects. They concluded that the elevated levels of sRAGE may be independently associated with severity of CAD and inflammation. It would have been useful to measure the plasma levels of AGE. It is possible that plasma levels of AGE are also elevated, and its elevation is greater than the elevation of sRAGE in these patients resulting in an increase in the ratio of AGE/sRAGE and hence adverse effects on coronary artery. They have measured S100A<sub>12</sub> a ligand for sRAGE. However, they did not provide the ratio of S100A<sub>12</sub>/sRAGE. Increase in the ratio of AGE/sRAGE has been reported to be risk factor/biomarker for diseases.<sup>25,98</sup> Park et al<sup>96</sup> have reported that plaque vulnerability was associated with increased levels of plasma sRAGE and MMP-9 in patients with acute myocardial infarction compared with control subjects. sRAGE is a protective biochemical and hence its increased levels should not be responsible for plaque vulnerability. Also increased levels of sRAGE are known to decrease the levels MMPs.<sup>99,100</sup> It is also possible that that AGE levels are elevated and the elevation is greater than sRAGE increasing the ratio of AGE/sRAGE that would increase the MMP levels.<sup>99</sup> It is known that AGE-RAGE interaction increases the generation of MMP-9 that in turn would produce plaque rupture. MMP-9 has been implicated in plaque rupture.<sup>57,58</sup> Raposeiras-Roubín et al<sup>80</sup> have reported that there were no significant differences in skin autofluorescence AGE and plasma sRAGE among unstable angina, STEMI and NSTEMI subjects at admission in the hospital. However, cardiac events (cardiac deaths, reinfarction, and new onset of heart failure) were associated with increased levels of sRAGE. In summary, serum levels of sRAGE were reduced in most patient but were elevated in some patients with CAD.

### Serum Levels of esRAGE in CAD Patients

Wagner et al<sup>101</sup> have reported that low plasma levels of esRAGE were associated with increased CV mortality, suggesting that esRAGE is better predictive marker than cRAGE alone. Increased levels of AGE and decreased levels of esRAGE are associated with angiographic severity and extent of CAD in patients with type 2 diabetes.<sup>75</sup> Lu et al<sup>102</sup> have shown that increased AGE and decreased esRAGE are associated with in-stent restenosis in Chinese diabetic patients. Elevated levels of serum AGE and reduced levels of serum sRAGE and esRAGE are associated with severity of albuminuria and postprocedural contrast-induced acute kidney injury, and exert a negative impact on 1-year clinical outcome in patients with type 2 diabetes undergoing PCI with Sirolimus-eluting stent implantation.<sup>103</sup> Yang et al<sup>104</sup> have reported that lower serum levels of esRAGE were associated with higher major cardiovascular events in patients with type 2 diabetes and stable CAD undergoing PCI. Serum levels of esRAGE are lower in patients with angiographically determined coronary plaque progression in diabetic patients,<sup>105</sup> and in subjects with greater atherosclerosis burden than control subjects.<sup>24,105,106</sup> Serum esRAGE has been reported to be lower in patients with type 2 diabetes and CAD

compared with control subjects, while there was no significant difference in these levels in patients with CAD in nondiabetic patients and control subjects.<sup>75</sup> However, Colhoun et al<sup>107</sup> reported an elevated level of serum esRAGE in patients with CAD. The above data suggest that the serum levels of esRAGE are reduced in patients with CAD with one exception. In summary, serum levels of esRAGE were lower in both the diabetic and nondiabetic patients with CAD.

### Expression of RAGE in CAD Patients

Expression of RAGE in coronary artery of CAD patients is not available in literature. However, Rodiño-Janeiro et al<sup>108</sup> have shown that RAGE expression in subcutaneous adipose tissue but not in epicardial adipose tissue is downregulated in patients with CAD as compared with those without CAD. RAGE expression is upregulated in atherosclerotic lesion. Expression of RAGE is elevated in carotid arterial wall of Zucker diabetic rats as compared with euglycemic control rats and the levels are further elevated in balloon-injured carotid artery of these rats.<sup>15</sup> Arterial de-endothelialization in wild-type mice increases the expression of RAGE in injured vessels.<sup>16</sup> Expression of RAGE in apoE  $-/-$  mice is significantly increased in atherosclerotic plaque.<sup>109</sup> These investigators also reported that the development of atherosclerosis was prevented in double knockout (apoE  $-/-$  /RAGE  $-/-$ ) diabetic mice. In apoE  $-/-$  and RAGE  $-/-$  (double knockout) mice, the plaque area is reduced.<sup>110</sup> Forbes et al<sup>111</sup> reported that the expression of RAGE is focally increased in atherosclerotic vascular disease. Blockade of RAGE expression with sRAGE or genetically RAGE deleted mice protected the ischemia-reperfusion myocardial injury.<sup>112,113</sup> In summary, RAGE expression was upregulated in atherosclerotic lesions in animal model of atherosclerosis and blockade of RAGE expression with sRAGE or genetically RAGE deletion (RAGE  $-/-$ ) prevented the development of atherosclerosis and ischemia reperfusion cardiac injury in mice. These data suggest that RAGE is involved in the genesis of atherosclerosis.

### AGE–RAGE Stress in CAD

There are limited reports on the AGE–RAGE stress in patients with CAD. McNair et al<sup>13</sup> measured the ratio of AGE/sRAGE (AGE–RAGE stress) in 46 men with NSTEMI and 28 control subjects and observed that AGE/sRAGE ratio were significantly higher in patients with NSTEMI compared with control subjects. They also reported that the ratio of AGE/sRAGE was significantly elevated to a similar degree in NSTEMI with 1 vessel, 2 vessels, and 3 vessels disease when compared with control subjects. McNair et al<sup>14</sup> investigated if post-PCI restenosis is associated with high AGE/sRAGE ratio and if pre-PCI and post-PCI levels of AGE/sRAGE were similar in patients with or without post-PCI restenosis in NSTEMI patients. They reported that pre-PCI ratio of AGE/sRAGE was greater in both groups of patients who developed or did not develop post-PCI restenosis as compared with control subjects, but the increases were more in post-PCI patients who developed restenosis than those who did not develop restenosis.

Hyperlipidemia is a risk factor for CAD. We<sup>114</sup> investigated if hyperlipidemia is associated with increased levels of AGE/sRAGE in 100 patients with NSTEMI and observed that there was a positive correlation of AGE/sRAGE with total cholesterol, triglycerides, and LDL-C levels, and negative correlation between HDL-C and AGE/sRAGE. Kazikawa et al<sup>115</sup> measured the endothelial cell dysfunction using flow mediated and nitroglycerine induced-vasodilation and AGE–sRAGE ratio in 110 subjects and concluded that AGE/sRAGE is an independent predictor of endothelial dysfunction. Endothelial dysfunction is precursor for atherosclerosis. The above data suggest that AGE–RAGE stress is involved in the CAD.

### Evidence for AGE–RAGE Stress-Induced Atherosclerosis

Evidences suggest that AGE–RAGE stress is involved in the development of atherosclerosis. AGE and RAGE levels are elevated in carotid arterial wall of Zucker diabetic rats as compared with euglycemic control rats and the levels of AGE and RAGE are further elevated in the balloon-injured carotid artery of these rats.<sup>15</sup> Administration of sRAGE before and for up to 21 days post-balloon injury significantly reduced neointimal hyperplasia and this was associated with decreases in vascular smooth muscle cell growth in vitro and vascular smooth muscle cell proliferation in vivo in these rats. Arterial de-endothelialization in wild-type mice increases the expression of RAGE in injured vessel, especially in smooth muscle cells, and increases deposition of AGE in expanding intima.<sup>16</sup> They demonstrated that administration sRAGE decreased neointimal hyperplasia, smooth muscle cell proliferation and migration, and expression of extracellular matrix protein. Atherosclerosis is accelerated in streptozotocin-induced diabetes in apoE-deficient mice and this effect was associated with increased expression of VCAM-1 in aorta when compared with nondiabetic mice.<sup>17</sup> These investigators also reported that administration of sRAGE significantly decreased the atherosclerotic lesion in a glycemic- and lipid-independent manner. Expression of RAGE and VCAM-1 was elevated in aorta of apo-E deficient diabetic rats and that expression of RAGE and VCAM-1 was downregulated with administration of sRAGE.<sup>116</sup> sRAGE has been reported to completely suppress accelerated and advanced atherosclerosis in apoE-deficient mice.<sup>18</sup> McNair et al<sup>13</sup> have reported that sRAGE levels are reduced in patients with NSTEMI. McNair et al<sup>14</sup> have also shown that reduced serum levels of sRAGE are a predictor of restenosis following PCI. Prasad<sup>117</sup> has discussed in detail the role of AGE and RAGE in the development and progression of carotid artery stenosis. AGE–RAGE axis may also play a role in the development of CAD.<sup>118</sup> It is to note that ROS also depresses myocardial contractility.<sup>119</sup> This effect of ROS would add to the cardiac effects of atherosclerosis. ROS is involved in the development of atherosclerosis.<sup>120–122</sup>

### Treatment Modalities for AGE–RAGE Stress-Induced CAD

Considering the involvement of AGE–RAGE axis in genesis of atherosclerosis (CAD), the treatment target should include

reduction in AGE, RAGE, and ROS levels, degradation of AGE in vivo, blocking of AGE-RAGE binding, and elevation of sRAGE. The treatment modalities for AGE-RAGE-induced diseases have been described in detail by Prasad and Tiwari<sup>123</sup> and Prasad and Bhanumathy.<sup>54</sup> A brief description of treatment of CAD is outlined below.

(a) AGE-reduction

AGE reduction in the body can be achieved by reduction in AGE intake, modification in food cooking, and other AGE lowering procedures.

1. Intake of AGE

AGE levels in the body can be lowered by reducing intake of food containing high amount of AGE (red meat, animal fat, cheese, and sweetened food).<sup>124</sup> The use of food such as grains, legumes, breads, vegetables, fruits, and low-fat milk that contain lowest amount of AGE<sup>125</sup> should be encouraged.

2. Food cooking

Cooking of food at low temperature in moist heat for short duration should be advised, because it reduces the formation of AGE.<sup>125</sup> Cooking at high temperature in dry heat (frying, broiling, grilling and roasting) increases formation of AGE.<sup>125</sup>

3. Other AGE lowering procedures

Cigarette smoking should be stopped because it increases the serum levels of AGE.<sup>126</sup> Exercise should be advocated because exercise reduces the AGE levels.<sup>127,128</sup> Sugar consumption should be reduced because it increases the formation of AGE.<sup>19,20</sup>

(b) Reduction in AGE formation

AGE formation can be reduced with vinegar, lemon juice, benfotiamine, pyridoxine, vitamins C, D and E,  $\alpha$ -lipoic acid, resveratrol, and curcumin.<sup>54,123</sup>

(c) Suppression of RAGE expression

RAGE expression is suppressed with the use of statins, candesartan, nifedipine, and rosiglitazone.<sup>54,117</sup>

(d) RAGE receptor blocker

Azeliragon has been used for AGE receptor blocker in patients with Alzheimer's disease.<sup>129</sup> It has not been tried in other diseases.

(e) Elevation of sRAGE

sRAGE levels can be increased by upregulating the expression of sRAGE and by exogenous administration. Expression of sRAGE can be upregulated with statins,<sup>130</sup> angiotensin converting enzyme inhibitors,<sup>131</sup> and rosiglitazone.<sup>132</sup> Exogenous administration of sRAGE has been successful in animal model of atherosclerosis.<sup>16,17,110,111</sup> It has not been tried in humans.

(f) AGE degrader in vivo

Glyoxalase-1 an endogenous enzymatic degrader of AGE has been described in detail by Prasad and Bhanumathy.<sup>54</sup> It has not available for use. However, it has been reported that the combined use of transresveratrol found in grapes and hesperidin found in orange increases the activity of glyoxalase-1 in placebo-control crossover clinical trial.<sup>133</sup> Considering this, grapes and oranges might be helpful in patients with CAD. AGE receptor-

mediated degrader of AGE (AGE receptor 1 [AGER1]) is not available in the market. It may serve as a future target for treatment of CAD.

(g) Antioxidants

Since ROS is generated with interaction of AGE and RAGE and ROS has been implicated in the development of atherosclerosis,<sup>120-122</sup> antioxidants may be helpful in AGE-RAGE stress-induced atherosclerosis and CAD. Antioxidant treatment in AGE-RAGE-induced atherosclerosis has been described in detail by Prasad and Bhanumathy.<sup>54</sup>

## Perspectives

CAD is due to coronary artery atherosclerosis and atherosclerotic plaque rupture resulting in coronary occlusion. AGE-RAGE axis plays a role in the development of atherosclerosis in numerous ways including reduction in the levels of NO that is known to protect atherosclerosis through vasodilation, and inhibits inflammatory mediators, platelet aggregation, and platelet activation,<sup>134,135</sup> enhancement of atherogenic activity of LDL,<sup>26</sup> decreasing the reverse cholesterol transport,<sup>136</sup> and production of ROS, NF- $\kappa$ B, cytokines, adhesion molecules, MCP-1, GM-CSF, and growth factors described in detail in the earlier section of this chapter.

AGE, RAGE, and sRAGE may play a role in the development of atherosclerosis<sup>9,54</sup> and plaque rupture<sup>55,56,58-64</sup> AGE levels in serum<sup>66-76</sup> and skin autofluorescence<sup>77-80</sup> in patients with CAD and expression of RAGE<sup>15,108-113</sup> in animal model of atherosclerosis are elevated, while serum sRAGE levels are reduced in patients with CAD. The serum levels of sRAGE in CAD patients are contradictory. The levels of sRAGE in patients with CAD have been reported to be reduced<sup>84-91</sup> in some and elevated<sup>92-96</sup> in others. The elevation of sRAGE could be due to patient selection. It is known that serum sRAGE are elevated in patients with diabetes 1<sup>136</sup> and diabetes 2,<sup>137</sup> and in patients with impaired renal disease especially with end-stage renal disease.<sup>138,139</sup>

sRAGE is antiatherogenic because it competes with RAGE for binding with AGE. It is known that atherosclerosis develops in diabetic patients in spite of high levels of sRAGE.<sup>23,140</sup> One would have expected that high levels of sRAGE would have protected the development of atherosclerosis in diabetic patients but it did not do so. The reason could be that elevation of AGE levels is greater than the elevation of sRAGE in diabetic patients. Hence, measurement of AGE and sRAGE in the same patient would be useful. This will allow to assess the AGE-RAGE stress that is ratio of AGE/sRAGE.<sup>25</sup> AGE-RAGE stress is a risk factor for disease and high AGE-RAGE stress indicates the presence and severity of the disease. AGE-RAGE axis comprises of four measurable components, AGE, RAGE, sRAGE, and esRAGE. Hence, measurement of only one of these parameters would not give a true biomarker/risk marker. RAGE measurement requires tissue that is not practical in patients. Simultaneous measurements of AGE and sRAGE should be performed to assess the AGE-RAGE stress (AGE/sRAGE). Very few investigations have been performed using AGE-RAGE stress to determine biomarker/risk marker for CAD.<sup>13,14,114,115</sup> It has been reported that AGE/sRAGE are elevated in patients

irrespective of low serum sRAGE in NSTEMI,<sup>13</sup> thoracic aortic aneurysm,<sup>99</sup> hyperthyroidism,<sup>141</sup> hypercholesterolemic patients,<sup>114</sup> and high serum levels of sRAGE in end-stage renal disease.<sup>139</sup> It is stressed that AGE, RAGE, sRAGE, or esRAGE individually cannot serve as biomarker/risk marker. AGE-RAGE stress is the best biomarker/risk marker of CAD.

Considering involvement of AGE-RAGE axis in the development of CAD some of the therapeutic interventions, such as reduction in AGE levels and prevention of AGE formation are easy to follow. Suppression of RAGE expression and elevation of sRAGE needs drugs that are being used for lowering cholesterol levels, antidiabetic agents, angiotensin converting enzyme inhibitor, and calcium channel blocker. Patients with CAD are usually are on one or more of these drugs and hence get benefit. Some the drugs such as AGE degraders, sRAGE, and RAGE blocker (Azelaic acid) are not available in the market for use in diseases except Alzheimer's disease.

## Conclusions

CAD is caused by atherosclerosis of coronary artery and rupture of atherosclerotic plaques. AGE-RAGE stress can induce atherosclerosis through generation of numerous atherogenic factors. Serum AGE in CAD patients, expression of RAGE in atherosclerotic lesion in animals, and AGE-RAGE stress in CAD patients are elevated but serum esRAGE levels are reduced in CAD patients. sRAGE levels are elevated in some while reduced in other CAD patients. Treatment of AGE-RAGE stress-induced atherosclerosis includes reduction in AGE intake, prevention of AGE formation, degradation of AGE in vivo, suppression of RAGE expression, blockade of AGE-RAGE binding, elevation of sRAGE, and use of antioxidants. Treatment modalities could prevent, regress, and slow the progression of CAD.

### Disclosure

None.

### Conflict of Interest

None declared.

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