

# Do Advanced Glycation End Products and Its Receptor Play a Role in Pathophysiology of Hypertension?

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## Abstract

There is a close relationship between arterial stiffness and blood pressure. The studies suggest that the advanced glycation end products (AGEs) and its cell receptor (RAGE) are involved in the arterial stiffness in two ways: changes in arterial structure and vascular function. Plasma levels of AGEs and expression of RAGE are elevated, while the levels of soluble RAGE (sRAGE) and endogenous secretory RAGE (esRAGE) are lowered in patients with hypertension (HTN). There is a positive correlation between plasma levels of AGEs and arterial stiffness, and an inverse association between arterial stiffness/HTN, and serum levels of sRAGE and esRAGE. Various measures can reduce the levels of AGEs and expression of RAGE, and elevate sRAGE. Arterial stiffness and blood pressure could be reduced by lowering the serum levels of AGEs, and increasing the levels of sRAGE. Levels of AGEs can be lowered by reducing the consumption of AGE-rich diet, short duration of cooking in moist heat at low temperature, and cessation of cigarette smoking. Drugs such as aminoguanidine, vitamins, angiotensin-converting enzyme (ACE) inhibitors, angiotensin-II receptor blockers, statins, and metformin inhibit AGE formation. Alagebrium, an AGE breakers reduces levels of AGEs. Clinical trials with some drugs tend to reduce stiffness. Systemic administration of sRAGE has beneficial effect in animal studies. In conclusion, AGE–RAGE axis is involved in arterial stiffness and HTN. The studies suggest that inhibition of AGEs formation, reduction of AGE consumption, blockade of AGE–RAGE interaction, suppression of RAGE expression, and exogenous administration of sRAGE may be novel therapeutic strategies for treatment of arterial stiffness and HTN.

## Keywords

- ▶ advanced glycation end products
- ▶ receptor for AGE
- ▶ soluble receptor for AGE
- ▶ hypertension
- ▶ arterial stiffness
- ▶ management of hypertension

Hypertension (HTN) accounts for 6% of death worldwide. The prevalence of HTN varies being lowest in rural India (3.4% in men and 6.8% in women), and highest in Poland (68.9% in men and 72.5% in women).<sup>1</sup> Prevalence of HTN was 27.1% in men and 30.1% in women in the adult population of United States.<sup>1</sup> HTN is a risk factor for cardiovascular diseases including stroke and myocardial infarction.

There are two types of HTN. Primary or essential which accounts for 90 to 95% and its etiology is not known. Secondary HTN which accounts for 5 to 10% and its etiology is known.

Advanced glycation end products (AGEs) and its cellular receptor (RAGE) may play a role in the pathophysiology of HTN. Interaction of AGEs with RAGE increases the expression and release of inflammatory cytokines, generation of reactive oxygen species (ROS), and activates nuclear factor kappa-B (NF-κB).<sup>2–4</sup> These agents might affect the structures of arterial wall and/or produce contraction of the arterial wall. Various measures are available for the prevention and treatment of HTN.<sup>5</sup> However, very little attention has been given to the role of AGEs and its receptors in initiation and maintenance of arterial stiffness and HTN.

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This review focuses on the mechanism of HTN especially systolic HTN, AGEs and RAGE axis, mechanism of AGE-RAGE axis in the development of HTN and arterial stiffness, effects of AGE and soluble receptors for AGE (sRAGE) on the elasticity of blood vessels, and measures to lower levels of AGEs and elevate the levels of sRAGE in blood in the management of arterial stiffness and HTN.

## Hypertension

In each cardiac cycle, the highest pressure is called systolic and the lowest pressure is called diastolic pressure. Systolic pressure is determined by stroke volume, peak systolic rate of cardiac ejection, and arterial compliance. The factors that determine the diastolic pressure include total peripheral vascular resistance, heart rate, systolic pressure, and arterial elastic recoil. Pulse pressure (PP) is the difference between systolic and diastolic pressures and is approximately half of the diastolic pressure.<sup>6</sup> PP depends on cardiac output, compliance of the central artery, and wave reflection. Both systolic and diastolic pressures increase with age. Diastolic pressure beyond the age of 50 to 60 years tends to plateau and even decrease with increasing age.<sup>7</sup> PP used as indicator of arterial stiffness has two problems: (1) PP is dependent on cardiac output and wave reflection and (2) physiological amplification occurs as the central arterial pressure wave propagates downward. High PP reflects systolic HTN and increased central arterial stiffness. Arterial stiffness increases systolic blood pressure that in turn increases left ventricular afterload and mass. It also lowers diastolic pressure resulting in decreased coronary artery perfusion. In adults older than 60 years of age, the PP of > 60 mm Hg is predictor of heart attack or other cardiovascular diseases. Wide PP is an indicator of not only the stiffness of artery but various other conditions.<sup>6</sup> High systolic and diastolic pressures 160/120 mm Hg indicate high risk than a pressure of 110/70 mm Hg even though the PP is similar (40 mm Hg) in both cases.

HTN is defined as systolic pressure of > 140 mm Hg and diastolic pressure of > 90 mm Hg. Isolated systolic HTN is defined as systolic pressure of > 140 mm Hg and diastolic pressure of < 90 mm Hg. It is most common form of HTN in people older than 50 years of age. Risk of high blood pressure increases with age and sex. Risk increases in men older than 45 years of age and women older than 55 years of age. Over half of Americans older than 60 years of age have HTN.

There are two types of HTN:

1. Essential, idiopathic, or primary HTN without known etiology. This type of HTN accounts for 90 to 95% of all HTN. The mechanism(s) of essential HTN is very complex because of numerous involved factors.
2. Secondary HTN with known causes comprise 5 to 10% of all HTN.

## Mechanism of Vascular Stiffness

Arterial stiffness depends on structural and functional components of artery. The arterial wall is composed of intima,

media, and adventitia. The intima consists of endothelium and thin basement membrane. Internal elastic lamina composed primarily of type IV collagen.<sup>8</sup> It very little adds to the elastic properties of the artery. The media is composed of elastin, collagen, smooth muscles, and ground substance called mucopolysaccharide gel. The ratio of elastin to collagen is highest in the aorta and decreases as one goes away from the heart to peripheral arteries. Smooth muscle cells in the artery increases as one goes away from the heart to peripheral arteries. The adventitia is composed of fibrous tissue. At low to normal arterial pressures, the stiffness is due to elastin fibers. However, at pressures (systolic > 200 mm Hg), collagen fibers contribute to stiffness.<sup>9</sup> Low ratio of elastin to collagen makes artery stiffer and vice versa. Endothelial signaling and vascular smooth muscle cell also affect vascular stiffness.<sup>10</sup> Clinical manifestation of arterial stiffness includes isolated systolic HTN (systolic pressure > 140 mm Hg and diastolic pressure < 90 mm Hg) and elevated PP.<sup>11</sup>

Collagen and elastin are regulated by matrix metalloproteinases (MMPs). MMPs degrade extracellular matrix by creating uncoiled less effective collagen and broken and frayed elastin molecules. Vascular cells and inflammatory cells including macrophages and polymorphonuclear leukocytes produce collagenases (MMP-1, MMP-8, and MMP-13) and elastases (MMP-7).<sup>12</sup> Structural changes including fragmentation of elastin, increased amount of collagen, arterial calcification, glycation of elastin and collagen, and cross-linking of collagen with AGEs leads to the stiffness of the artery.<sup>13,14</sup> Isolated systolic HTN, elevated PP, and increased pulse wave velocity (PWV) are risk for strokes, myocardial infarction, heart failure, and overall mortality rate in older adults.<sup>9</sup> For every 2 mm Hg increase in systolic pressure, there is an increase in the risk of fatal stroke by 7% and fatal coronary heart disease event by 5%.<sup>15</sup> Besides structural changes in the central arteries, there are other factors that contribute to the stiffness of the central arteries. These factors include endothelial dysfunction, neuroendocrine signaling, high glucose, insulin resistance, and genetic predisposition. Endothelial dysfunction contributes to the arterial stiffness through imbalance between vasodilator nitric oxide (NO) and vasoconstrictors (hormones, cyclooxygenase, nicotine adenine dinucleotide phosphate oxidase, and xanthine oxidase).<sup>10,16</sup> Zieman et al<sup>10</sup> have suggested that the compliance of the arterial wall affects endothelial mechanotransduction and that the rigidity of wall might decrease the endothelial NO synthase (eNOS) activity resulting in arterial stiffness.

Neuroendocrine factors include angiotensin II and aldosterone. Angiotensin II increases the formation of collagen, triggers matrix remodeling and vascular hypertrophy, suppresses NO-dependent signaling, increases ROS generation, and reduces synthesis of elastin,<sup>16,17</sup> ROS has been suggested to be involved in the angiotensin II-induced HTN.<sup>18</sup> Aldosterone induces stiffness in the arterial wall through fibrosis and expression of fibronectin, and hypertrophy of vascular smooth cells.<sup>19</sup>

Clinically, arterial stiffness is measured by PWV and augmentation index (AIx). PWV is the rate at which pressure

wave moves downward along the artery. This measurement gives arterial compliance/stiffness. An increase in the PWV indicates an increase in the arterial stiffness. PWV depends on arterial stiffness, ventricular ejection length, and peripheral vascular resistance. PWV is calculated as distance traveled by the arterial pulse wave divided by the time delay between two arterial points. Alx is a measure of enhancement of central aortic pressure by reflective wave and is a measure of arterial stiffness. It is calculated by the ratio of augmentation pressure to PP and expressed as percentage (%). Increase in Alx indicates an increase in arterial stiffness.

## AGE-RAGE Axis

AGEs are heterogenous group of irreversible adducts formed by the nonenzymatic glycation and glycooxidation of proteins, nucleic acid, and lipids with reducing sugars.<sup>20,21</sup> There are three receptors for AGEs: full length RAGE, N-truncated RAGE, and C-terminal RAGE which has two isoforms, cleaved RAGE (cRAGE) and endogenous secretory RAGE (esRAGE). cRAGE is proteolytically cleaved from full length RAGE.<sup>22</sup> esRAGE is produced from alternative messenger RNA splicing of full length RAGE.<sup>23</sup> Total soluble RAGE (sRAGE) includes cRAGE and esRAGE. esRAGE is approximately 20 to 30% of the total sRAGE.<sup>24,25</sup> Full length RAGE is a multiligand cell bound receptor, while esRAGE and sRAGE circulate in the blood. Interaction of AGEs with full length RAGE activates NF- $\kappa$ B, increases the gene expression and release of inflammatory cytokines, and increases production of ROS.<sup>3,4,26</sup> sRAGE and esRAGE act as a decoy for RAGE by binding with RAGE ligand, and thus have protective effects against deleterious effects of interaction of AGEs with RAGE.<sup>27</sup> Hyperglycemia in diabetes increases the levels of AGEs in the serum and tissue.<sup>28</sup> Oxidative stress increases the formation of AGEs.<sup>29</sup> Certain diets, cooking at high temperature and cigarette smoking also increase the serum levels of AGEs.<sup>30,31</sup>

## Mechanism of AGE-Induced Hypertension

AGEs can induce HTN in two ways: alteration in arterial compliance/stiffness and interaction of AGEs with RAGE on cell surface resulting in changes in cell function.

### Alteration in Arterial Stiffness

Causes of increased stiffness are fragmentation of elastin, increased amount of collagen, glycation of elastin, collagen, and cross-linking of collagen with AGEs. Arterial stiffness is composed of two components: structural and dynamic. Structural component comprises extracellular matrix (elastin and collagen). The dynamic component is the tone in the arterial smooth muscle which is dependent on endothelial cell function. Endothelium releases vasoactive substances such as NO and endothelin-1.

AGEs are formed in the proteins of extracellular matrix. Accumulation of AGEs on protein of extracellular matrix leads to the formation of cross-links, which trap other local macro-

molecules.<sup>32</sup> The properties of collagen are altered through AGE-RAGE intermolecular covalent bond or cross-linking.<sup>33</sup> Cross-linking of AGE on collagen and elastin increases the extracellular matrix area which increases the stiffness of the artery.<sup>34</sup> Glycation increases the synthesis of collagen.<sup>35</sup> Cross-linking make the collagen insoluble to hydrolytic enzymes.<sup>36</sup> AGE-linked collagen is less susceptible to hydrolytic turn over and is stiffer. There is a cross-linking of AGE with elastin which reduces the elasticity of the arterial wall. Cross-linking increases the amount of collagen and decreases the amount of elastin in the arterial wall.

Other mechanisms such as reduced NO and increased endothelin-1, neuroendocrine signaling, and impaired glucose tolerance besides structural changes in the artery (collagen and elastin fibers) may be involved in the arterial stiffness by AGEs.

AGEs reduce the bioavailability and activity of NO through various mechanisms. Matrix-bound AGEs inhibit antiproliferative activity of NO,<sup>37</sup> reduce the half-life of NO synthase (eNOS),<sup>38</sup> impair NO production,<sup>39</sup> quench and inactivate NO,<sup>40</sup> reduce production of prostacyclin,<sup>41</sup> and increase the expression of endothelin-1.<sup>42</sup> Impaired glucose tolerance enhances nonenzymatic glycation of proteins with covalent cross-linking of collagen and alters the mechanical properties of interstitial tissue of arterial walls.<sup>10</sup>

Neuroendocrine signaling can also affect the arterial stiffness. Angiotensin-II increases the formation of AGE and vice versa.<sup>43</sup> Increased levels of angiotensin can then increase the arterial stiffness through AGE or through release of oxygen radicals by interaction of AGE with RAGE. Angiotensin can increase oxygen radicals through various ways.<sup>18</sup> ROS degrades the elastin molecules in vitro.<sup>44</sup> ROS can modify newly synthesized tropoelastin and impair the assembly of tropoelastin into elastin fibers.<sup>45</sup> AGEs may contribute to endothelial dysfunction and vascular stiffness.

### Interaction of AGEs with RAGE Resulting in Changes in Vascular Functions

As mentioned earlier, interaction of AGE with RAGE increases the production of ROS, such as superoxide anion ( $O_2^-$ ), hydrogen peroxide ( $H_2O_2$ ) and hydroxyl radicals ( $\bullet OH$ ). Superoxide anions produces contraction of the isolated rabbit aorta that is endothelium dependent and is partially mediated by an arachidonic acid metabolism.<sup>46</sup>  $H_2O_2$  in lower concentration produces contraction, while in higher concentration, it produces transient relaxation followed by contraction of isolated rabbit aorta.<sup>47</sup> In vivo, in canine model, ROS generated by polymorphonuclear leukocytes and administration of oxygen radical increase total peripheral vascular resistance.<sup>48,49</sup> These data suggest that AGEs, through production of ROS, may induce HTN irrespective of arterial stiffness.

### Consequences of Arterial Stiffness with AGEs

Although arterial stiffness, length of ejection of stroke volume, and peripheral vascular resistance contribute to

systolic pressure, this pressure is mostly affected by arterial stiffness. Stiffness of large arteries has numerous consequences. Arterial stiffness with aging leads to isolated systolic HTN. Systolic pressure increases, while diastolic pressure increases till the age of 50 years after which diastolic pressure decreases.<sup>50</sup> Systolic HTN affects more than 50% individuals older than 60 years of age. Isolated systolic HTN is most common type of HTN among the elderly individuals. High systolic pressure induces left ventricular hypertrophy (LVH) and diastolic dysfunction. The incidence of these complications of systolic HTN doubles in individuals with isolated systolic HTN.<sup>51</sup> It is a major risk factor for stroke and ischemic heart disease.<sup>51</sup> Low diastolic pressure decreases the coronary artery perfusion and hence can induce ischemia in the heart. Lewington et al<sup>15</sup> have reported that for every 2 mm Hg increase in systolic pressure increases the risk of stroke by 7% and fatal ischemic heart disease events by 5%.

### Levels of AGEs, sRAGE, and esRAGE in Arterial Stiffness/Hypertension

Since AGEs have been reported to increase the stiffness of arterial wall and systolic blood pressure, and since the ROS produced by interaction of AGEs with RAGE produces vascular contraction, one would expect increases in the serum levels of AGEs, and decreases in the levels of sRAGE and esRAGE.

#### Serum Levels of AGEs and Arterial Stiffness/Hypertension

Plasma levels of methylglyoxal (MG), a source of AGE, were elevated in spontaneously hypertensive rats (SHR) in comparison to normotensive Wistar-Kyoto rats.<sup>52</sup> The increases in MG were positively correlated with the age of the SHR. McNulty et al<sup>53</sup> have reported that the plasma levels of AGEs were significantly higher in untreated hypertensive patients than in normotensive subjects ( $7.84 \pm 0.94$  vs.  $2.97 \pm 0.94$   $\mu\text{g/mL}$ ).

#### Serum Levels of sRAGE and Arterial Stiffness/Hypertension

Liu et al<sup>50</sup> measured the serum levels of sRAGE in 209 patients with essential HTN and showed that these patients had lower serum levels of sRAGE those with LVH than without LVH. Serum sRAGE levels were measured in 1,077 subjects from general population by Mayer et al.<sup>54</sup> They showed that the levels of sRAGE were lower in nondiabetic hypertensive patients. Heidland et al<sup>55</sup> have reported that plasma levels of sRAGE are lower in patients with essential HTN. Geroldi et al,<sup>56</sup> on the contrary, in a cross-sectional case-control study with never treated patients of essential HTN and normotensive, showed a weak association between sRAGE and systolic blood pressure. The association between sRAGE and PP, however, was very strong. The data on the whole suggest that serum sRAGE levels are low in patients with HTN /arterial stiffness.

#### Serum Levels of esRAGE and Arterial Stiffness/Hypertension

Koyama et al<sup>57</sup> have shown that the levels of esRAGE are lower in patients with HTN.

### Relationship between Serum AGEs and Hypertension/Arterial Stiffness

In the previous section, we have described that the serum levels of AGEs are elevated in the hypertensive patients or in the patients with arterial stiffness. In this section, we assess if there is a correlation between the levels of serum AGEs and HTN/arterial stiffness. McNulty et al<sup>53</sup> reported that there was a positive correlation between the plasma levels of AGEs and aortic PWV, an indicator of arterial stiffness in hypertensive patients. However, there was no correlation between plasma AGEs and Alx. This may be because of the fact that Alx reflects not only the stiffness of smaller muscular arteries but also the microvascular density, and number and location of terminal arterioles that contribute to reflected waves, in addition to velocity of pressure wave and left ventricular ejection pattern. Semba et al<sup>58</sup> reported that PP was positively associated with AGEs in young type 1 diabetics. They also showed that the plasma levels of N-epsilon-carboxymethyl-lysine (CML) and N-epsilon-carboxyethyl-lysine were positively associated with systolic pressure and negatively associated with diastolic pressure. However, there was no association of AGEs with mean arterial pressure. This could be because of increased PP. Semba et al,<sup>59</sup> in a longitudinal study of aging 493 subjects, showed that serum levels of AGEs are associated with increased aortic stiffness (PWV and PP). Llauradó et al<sup>60</sup> investigated the relationship of AGEs with arterial stiffness in patients with type 1 diabetes without clinical cardiovascular disease. They showed that elevated levels of AGEs were associated with arterial stiffness independent of cardiovascular risk factors, glycemic control, disease duration, and low grade inflammation. Sourris et al<sup>61</sup> reported that plasma levels of CML (AGE) were inversely related to the diastolic pressure after adjustment for age, sex, body mass index, and waist-hip ratio. AGEs levels were positively correlated with PP. However, there was no correlation between AGE and systolic pressure. Huang et al<sup>62</sup> investigated the relationship between AGEs and arterial stiffness in 1,051 Chinese participants which include 390 hypertensive patients. They showed that the plasma levels of AGEs were associated with stiffness in the carotid and femoral arteries assessed by PWV. This association of AGEs with PWV was stronger in hypertensive patients. They also showed that the levels of AGEs were significantly associated with central and peripheral Alx. However, Won et al<sup>63</sup> reported no association between serum AGEs and brachial-ankle PWV. These differences might be due to differences in the study population. In general, the data suggest that there is a positive association between serum levels of AGEs and arterial stiffness/HTN.

## Relationship between Serum sRAGE and Hypertension/Arterial Stiffness

Mayer et al<sup>54</sup> in general population showed that low levels of serum sRAGE were independently associated with increased arterial stiffness (increased PWV). This association was significant in nondiabetic patients with HTN.

Dimitriadis et al<sup>64</sup> in a study of untreated newly diagnosed 430 patients with essential HTN reported that there was an inverse relationship between serum sRAGE and carotid-femoral PWV. Geroldi et al<sup>56</sup> reported an inverse correlation between sRAGE and systolic pressure, and sRAGE and PP in nondiabetic essential hypertensive patients. However, there are few reports that show a positive correlation between sRAGE and arterial stiffness in type 2 diabetic patients.<sup>65</sup> In a study of 415 hypertensive patients with diabetes (107 patients), there was a positive correlation between serum sRAGE and arterial stiffness.<sup>66</sup> These data suggest that there is an inverse association between sRAGE and arterial stiffness in patients with HTN without diabetes, and a positive correlation between sRAGE and arterial stiffness in hypertensive patients with diabetes. This discrepancy could be due to the presence of diabetes in hypertensive patients. It is known that the levels of AGEs<sup>67,68</sup> and sRAGE<sup>69,70</sup> are elevated in patients with diabetes. It is possible that levels of AGEs are elevated more than the levels of sRAGE. If that is the case, then AGEs will have effect on structural changes in extracellular matrix and hence arterial stiffness in spite of increased levels of sRAGE in diabetic patients. A consideration should be given to both AGEs and sRAGE (or esRAGE) in the assessment of arterial stiffness instead of low sRAGE or high AGEs level alone. It has been suggested by Prasad<sup>71</sup> that the ratio of AGEs/sRAGE and AGEs/esRAGE should be considered as universal risk marker for diseases.

## Relationship between esRAGE and Hypertension/Arterial Stiffness

Ghanayem et al<sup>72</sup> showed that there was a significant correlation between the serum levels of esRAGE and systolic and diastolic blood pressure in patients with HTN. Koyama et al<sup>24</sup> showed that the plasma levels of esRAGE were inversely related to blood pressure in diabetic patients with metabolic syndrome. Humpert et al<sup>73</sup> reported that there was no correlation between serum levels of esRAGE and carotid intima-media thickness (IMT). However, Koyama et al<sup>24</sup> showed a weak association between serum levels of esRAGE and IMT. Choi et al<sup>74</sup> showed a negative correlation between serum levels of esRAGE and systolic and diastolic blood pressure in diabetic patients treated with diet alone and metformin or sulfonylurea. esRAGE did not show any correlation with ankle-brachial PWV. It has also been reported that esRAGE was inversely related to IMT.<sup>75</sup> It has been shown that the serum levels of esRAGE are inversely associated with the blood pressure, especially systolic in male nondiabetic patients with obstructive sleep apnea.

These data suggest that, in general, low levels of esRAGE are associated with arterial stiffness and HTN.

## Therapeutic Interventions for Arterial Stiffness/Hypertension

HTN and arterial stiffness interact with each other in a bidirectional manner.<sup>76,77</sup> Arterial stiffness and HTN are closely associated with age.<sup>8</sup> Considering the above concept, reduction in the levels of AGEs, suppression of expression of RAGE, and elevation of the levels of sRAGE and esRAGE would decrease the arterial stiffness and blood pressure. Since the interaction of AGEs with RAGE increases the formation of ROS which constricts the blood vessels, the lowering of the levels of AGEs and increasing the levels of sRAGE or esRAGE would reduce the blood pressure. The following measures should be taken to reduce the levels of AGEs, suppress the expression of RAGE, and increase the levels of sRAGE and esRAGE.

### 1. Reduction in consumption of AGEs

#### (a) Reduction in consumption of AGE-rich diet

The consumption of glucose should be reduced because glucose is involved in the formation of AGEs.<sup>20</sup> Consumption of some foods such as red meat, cheese, cream, butter, animal fat, and sweetened fatty cookies which are high in AGEs should be reduced.<sup>78</sup> It has been reported that diets such as butter, cream, cheese, margarine, and mayonnaise have highest amount of AGEs than oil and nuts.<sup>79</sup> Uribarri et al<sup>79</sup> also reported that among the meat group, beef has the highest amount of AGEs, followed by poultry, pork, fish, and eggs. The lowest amounts of AGEs are present in grains, legumes, breads, vegetables, fruits, and milk. Fat-free milk has lower AGEs than the whole milk.

#### (b) Cooking

Uriharri et al<sup>79</sup> reported that cooking at high temperature in dry heat increases the formation of AGEs. Frying, boiling, grilling, and roasting produce more AGEs than poaching, stewing, steaming, and boiling. Uribarri et al<sup>79</sup> also showed that short duration cooking in moist heat at low temperature reduces the formation of AGEs.

Only 10% of the diet-derived AGEs are absorbed from gastrointestinal tract and a significant amount remains in the body for 3 days after ingestion.<sup>80</sup> Short-term restriction of consumption of AGEs in diet in healthy or diabetic individuals significantly decreased the serum levels of AGEs.<sup>81</sup> Diet low in AGEs given for 2 months to mice reduced the serum levels of AGEs.<sup>82</sup>

#### (c) Cessation of cigarette smoking is beneficial because cigarette smoking increases the levels of AGEs.<sup>31</sup>

### 2. Prevention of formation of AGEs

#### (a) Acidic ingredients (lemon juice, vinegar)<sup>83</sup> and pomegranate<sup>84</sup> inhibits AGE formation.

#### (b) Pharmacological agents to prevent AGE formation:

##### (i) Aminoguanidine

Aminoguanidine (pimagedine), a hydralazine compound inhibits formation of AGE by acting as nucleophilic trap for carbonyl intermediates.<sup>85</sup> It has been

shown to prevent diabetic vascular complications in animal model of diabetes.<sup>86</sup> It reduces AGE hemoglobin independent of reduction of HbA<sub>1c</sub> in clinical trial.<sup>87</sup> In a placebo controlled clinical trial, aminoguanidine reduced glomerular filtration rate and urinary proteinuria, and prevented deterioration of retinopathy.<sup>88</sup> Further clinical trials of aminoguanidine were terminated due to concerns over long-term toxicity such as patients developing myeloperoxidase and antineutrophil antibodies and glomerulonephritis.<sup>89</sup>

#### (i) Vitamins

Vitamins may be potential therapeutic agents to inhibit the formation of AGEs. Pyridoxamine, a natural form of vitamin B<sub>6</sub>,<sup>90</sup> benfotiamine (vitamin B<sub>1</sub>),<sup>91</sup> vitamin C,<sup>92</sup> vitamin D,<sup>93</sup> and vitamin E<sup>94</sup> decrease the formation of AGEs. Pyridoxamine is effective in suppression of renal disease in streptozotocin-induced type 1 diabetes.<sup>90</sup> Vitamin E reduces the serum levels of AGEs in patients on dialysis.<sup>94</sup> Individuals with vitamin D deficiency have higher blood pressure.<sup>95</sup> It is possible that vitamin D-induced lowering of blood pressure is due to lowering of AGE formation.

#### (iii) Drugs

Angiotensin converting enzyme (ACE) inhibitor ramipril used for 2 months in patients with diabetes reduced fluorescent AGEs.<sup>96</sup> Angiotensin II receptor blockers telmisartan and losartan suppressed the formation of AGEs in cell culture.<sup>97</sup> Valsartan administered for 1 year in patients with HTN and diabetes reduced the serum levels of AGEs.<sup>98</sup> Candesartan administered to patients with HTN with diabetes for 3 months reduced the levels of AGEs (CML).<sup>99</sup>

Carvastatin administered to patients with diabetes or prediabetes for 3 months reduced the serum levels of AGEs.<sup>100</sup> Atorvastatin treatment reduced the serum levels of AGEs.<sup>101</sup>

Thiazolidine-derivative metformin reduces the levels of AGEs in women with polycystic ovary syndrome.<sup>102</sup> Other potential inhibitor for AGE formation include  $\alpha$  lipoic acid,<sup>103</sup> taurine,<sup>104</sup> aspirin,<sup>105</sup> pioglitazone,<sup>106</sup> pentoxifylline,<sup>106</sup> resveratrol,<sup>107</sup> and curcumin.<sup>108</sup>

### 3. AGE breakers

Alagebrium (3-phenacyl-4,5-dimethylthiazolium chloride, ALT-711) nonenzymatically breaks the established cross-linking of AGE with adjacent long lived collagen and elastin.<sup>109</sup> Studies in animals have shown the beneficial effects of alagebrium on arterial stiffness. Wolffenbuttel et al<sup>110</sup> have shown that large artery stiffness in streptozotocin-induced diabetic rats was reversed by alagebrium. Alagebrium reduced both aortic stiffness and A1x in old normotensive monkey.<sup>111</sup> Alagebrium reduced PWV and PP without reduction in mean arterial pressure.<sup>112</sup>

Clinical trial in human with alagebrium has positive results. Alagebrium, 200 mg twice daily for 8 weeks in men

with HTN on antihypertensive therapy reduced arterial stiffness by 37% and blood pressure by 6.8 mm Hg and these changes were associated with reduction in fibrosis of the blood vessels.<sup>10,113</sup> Kass et al<sup>112</sup> reported that in a double-blind clinical trial, alagebrium (210 mg/d for 8 weeks) administered to patients with systolic HTN increased total arterial compliance by 15% and reduced PP by 5.3 mm Hg. Systolic and Pulse Pressure Hemodynamics Improvement by Restoring Elasticity (SAPPHIRE) study has also shown the beneficial effects of alagebrium in systolic HTN.<sup>113</sup>

## Downregulation of RAGE Expression

Downregulation of expression of RAGE would reduce the arterial stiffness and blood pressure. There are numerous agents that can downregulate the expression of RAGE. Simvastatin inhibits the expression of RAGE through a decrease in myeloperoxidase-dependent production of AGEs.<sup>114</sup> Atorvastatin downregulates the expression of RAGE in vitro.<sup>115</sup> Angiotensin II receptor blockers, telmisartan, and candesartan downregulates the RAGE expression.<sup>116,117</sup> Thiazolidinediones reduce the expression of RAGE in the endothelium.<sup>118</sup> Curcumin downregulates the expression of RAGE in cultured hepatic cells.<sup>119</sup> Calcium channel blocker, nifedipine suppresses the expression of RAGE in the endothelial cells exposed to AGEs.<sup>120</sup>

## Elevation of the Levels of sRAGE and esRAGE

### Statins

Treatment with pitavastatin and pravastatin increased the serum levels of sRAGE in humans.<sup>101</sup> Atorvastatin, fluvastatin, and lovastatin increase the serum levels of sRAGE in isolated cell lines.<sup>121</sup> Atorvastatin increases the levels of sRAGE and esRAGE in vitro.<sup>121,122</sup>

### ACE Inhibitors

Ramiprilat increased the expression of sRAGE in the aorta of streptozotocin-induced diabetic rats.<sup>123</sup> Forbes et al<sup>123</sup> also reported that ramipril significantly increased the serum, a level of sRAGE in diabetic rats. Perindopril elevated the levels of serum sRAGE in patients with type 1 diabetes.<sup>123</sup>

### Angiotensin II Receptor Blocker

Telmisartan reduces the serum levels of sRAGE by decreasing its secretion.<sup>116</sup>

### Antidiabetic Drug

Tan et al<sup>124</sup> reported an increase in the serum levels of sRAGE and esRAGE with rosiglitazone in patients with type 2 diabetes.

### Systemic Administration of Recombinant sRAGE

The studies indicate that the elevated levels of serum sRAGE are associated with an improvement in arterial stiffness and isolated systemic HTN. Exogenous administration of recombinant sRAGE should ameliorate the arterial stiffness and HTN. Tang et al<sup>125</sup> have reported that administration of

recombinant sRAGE protected ischemic stroke in animal model. Administration of exogenous sRAGE reduced the carotid artery restenosis in mice,<sup>126</sup> AGE-induced vasculopathy in diabetic rats,<sup>127</sup> and completely suppressed atherosclerosis in apolipoprotein E-deficient mice.<sup>128</sup>

These observations suggest the possibility of exogenous administration of recombinant sRAGE is to raise the serum levels of sRAGE and reduce the arterial stiffness and high blood pressure especially old age isolated systemic HTN. However, till now, no data are available on the exogenous administration of recombinant sRAGE in patients with arterial stiffness and HTN.

### Effects of Therapeutic Interventions on Arterial Stiffness/Hypertension

Statins, which reduces the levels of AGEs and raises the levels of sRAGE, also reduces the arterial stiffness. Atorvastatin (10 mg/daily) produced improvement in arterial stiffness in hypertensive and hypercholesteremic subject.<sup>129</sup> Atorvastatin improved the arterial stiffness in patients with ischemic heart disease.<sup>130</sup> Fluvastatin had variable effects on arterial stiffness. Rizos et al<sup>131</sup> reviewed nine control randomized trials with fluvastatin on arterial stiffness. Fluvastatin in two studies showed a decrease in central aortic PWV (caPWV), in one study, there was no change in caPWV and in other study, there was an increase in caPWV. In other five studies, fluvastatin reduced the brachial artery PWV.

Antidiabetic drug, pioglitazone, reduced arterial stiffness in diabetic patients.<sup>132</sup> Rosiglitazone had variable effects on PWV, decreases<sup>133</sup> in one and no improvement in the other.<sup>134</sup> Metformin reduced arterial stiffness in young women with polycystic ovary syndrome.<sup>135</sup>

Aminoguanidine decreased arterial stiffness in old rats,<sup>136</sup> streptozotocin-induced diabetic rats,<sup>137</sup> and in humans.<sup>138</sup> Alagebrium reduced arterial stiffness in older monkeys,<sup>111</sup> in older patients with isolated systolic HTN,<sup>112</sup> and in rat aging model.<sup>139</sup>

### Perspectives

Arterial stiffness and blood pressure pulsation are related. It is, however, not fully understood if there is a temporal relationship between arterial stiffness and elevation of blood pressure. Kaess et al<sup>140</sup> have shown that high aortic stiffness was associated with higher risk of incident HTN. These investigators also reported that initial blood pressure was not associated with progressive aortic stiffness. It has been, however, reported that aortic stiffness is greatly associated with age, HTN, obesity, impaired glucose tolerance, and dyslipidemia.<sup>141,142</sup> As mentioned earlier,<sup>76,77</sup> HTN and arterial stiffness functionally interact bidirectionally. It has been suggested that arterial stiffness should be taken into consideration in the management of HTN.<sup>143</sup> Arterial stiffness may be causal factor for HTN because PWV is elevated even when the arterial pressure is at borderline of HTN.<sup>144</sup>

Traditional antihypertensive drugs such as ACE inhibitors, angiotensin II type 2 receptor antagonists, and  $\beta$  blockers

reduce the arterial stiffness indirectly by lowering blood pressure but not through changes in the extracellular matrix. AGE-RAGE axis may be involved in the pathogenesis of essential HTN, and hence, the treatment target for essential HTN should include the agents that prevent the AGE-induced degradation of elastic fibers and formation of collagen fibers. Inhibition of AGE formation, blockade of AGE-RAGE interaction, and suppression of RAGE expression may be novel therapeutic strategies for treatment of arterial stiffness and HTN.

### Conclusion

In conclusion, the data suggest that AGE-RAGE axis is involved in the development of arterial stiffness and HTN especially isolated systolic HTN. The studies also suggest that reduction of AGE formation and consumption, suppression of RAGE expression, elevation of sRAGE, and exogenous administration of recombinant sRAGE may be novel therapeutic strategies for the management of arterial stiffness/HTN. It will be of benefit to add these new therapeutic agents in addition to traditional antihypertensive agents in the management of arterial stiffness, increased PP, and HTN.

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