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Review

AGE-RAGE stress play a role in aortic aneurysm: A comprehensive review and novel potential therapeutic target

Kailash Prasad *

Department of Physiology (APP), College of Medicine, University of Saskatchewan, Saskatoon, SK, Canada, S7N 5E5, Canada

*Correspondence: k.prasad@usask.ca (Kailash Prasad)

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Aortic aneurysms are mostly asymptomatic but have high rates of mortality when there is rupture or dissection. Matrix metalloproteinases is involved in the evolution of aortic aneurysms. Advanced glycation end products and its cell receptor RAGE (receptor for AGE) and sRAGE (soluble receptor of AGE) have been suggested to be involved in the pathogenesis of numerous diseases. This review addresses the role of AGE, RAGE and AGE-RAGE stress (AGE/sRAGE) in the pathogenesis of abdominal aortic aneurysm and thoracic aortic aneurysm in humans. AGE-RAGE interaction not only increases the generation of reactive oxygen species and inflammatory cytokines, but also activates NF-kB. There are increases in the levels of AGE in aortic tissue, skin and serum in patients with thoracic aortic aneurysm and abdominal aortic aneurysm. Levels of RAGE in tissue are elevated in abdominal aortic aneurysm. AGE-RAGE stress is elevated in patients with thoracic aortic aneurysm. The serum levels of cytokines and Matrix metalloproteinases are elevated in patients with thoracic aortic aneurysm and abdominal aortic aneurysm. The levels of AGE and AGE-RAGE stress correlate positively with cytokines and Matrix metalloproteinases, but the serum levels of sRAGE correlate negatively with cytokines and Matrix metalloproteinases. Cytokines levels are positively correlated with the levels of Matrix metalloproteinases in patients with thoracic aortic aneurysm. In conclusion, elevated levels of AGE, RAGE and AGE-RAGE stress, and reduced levels of sRAGE increase the levels of cytokines that in turn increase the production of Matrix metalloproteinases resulting in formation of aortic aneurysms. The data suggest that AGE-RAGE stress is involved in the pathogenesis of aortic aneurysms. Treatment options have also been discussed.

Keywords

Aortic aneurysms; AGE; RAGE; AGE-RAGE stress; cytokines; matrix metalloproteinase

1. Introduction

Aortic aneurysm (AA) is a dilatation of aorta due to aortic wall weakness. In most cases AA is asymptomatic and is mentioned as a silent killer (Elefteriades, 2005). It is however associated with high rates of mortality especially when there is rupture of aortic aneurysm or dissection (Hudson et al., 2005). It has been reported by the center for Disease Control and Prevention that approximately 13000 people die of AA in various location in aorta (Control NCfIPa, 2012). Rupture of aortic aneurysm is generally an emergency situation and approximately 80% of death occurs in people of age 65 yrs and over (Reimerink et al., 2013). AA is the 19th leading cause of death in all individuals and is the 15th most common in individuals over 65 yrs. of age. Abdominal aortic aneurysm (AAA) is an important cause of cardiovascular mortality and is 15th leading cause of death from any cause in men over 55 yrs. of age (Xu et al., 2016). Aneurysm occurs both in thoracic and abdominal part of aorta, the most frequent localization being the abdominal infrarenal aorta. Although thoracic aortic aneurysm (TAA) and abdominal aortic aneurysm AAA) possess common mechanisms, they both have some distinct features (Guo et al., 2006). AAA is multifactorial disease connected with aging (Nordon et al., 2011), male gender (Svensjö et al., 2013), cigarette smoking (Forsdahl et al., 2009), visceral obesity (Sidloff et al., 2014), genetics (Larsson et al., 2009) and hypertension (Forsdahl et al., 2009). AAA is not associated with diabetes mellitus (Kent et al., 2010). The characteristic features of the wall of the aneurysm are chronic inflammation (Freestone et al., 1995), loss of extracellular protein elastin (Huffman et al., 2000), protease-mediated degradation of structural matrix proteins (Thompson et al., 2006), elevated activities of MMPs (MMP-2 and MMP-9) (Sinha and Frishman, 1998), increased neoangiogenesis (Thompson et al., 1996), enhanced oxidative stress (Zhang et al., 2003), infiltration of inflammatory cells and apoptosis of vascular smooth muscle cells (Ocana et al., 2003). The precise mechanism of aortic mechanism is still unknown. MMP-9 degrades extracellular matrix elastin and collagen (Freestone et al., 1995; Kuzuya and Iguchi, 2003). MMP-2 MMP-3, andMMP-9 which possess elastolytic and collagenolytic activities, are involved in the development of aortic aneurysm (Ailawadi et al., 2003; Kotze and Ahmad, 2011; Rabkin, 2017). Inflammatory cytokines are increased

in patients with abdominal aortic aneurysm (Juvonen et al., 1997). The expression of MMP-2 is elevated with IL-1β and TNF-α (Han et al., 2001). The expression of MMP-2 and MMP-3 is regulated by IL-1β (Mountain et al., 2007), IL-2 (Edsparr et al., 2010), IL-6 (Kusano et al., 1998) and TNF-α (Wong et al., 2001). It appears that inflammatory cytokines are the intermediatory in the stimulation of MMPs, which in turn destroy the extracellular matrix culminating in the formation of aortic aneurysm.

Advanced glycation end products (AGE) and its receptors have been implicated in the pathophysiology of various diseases including, non-ST-elevation myocardial infarction (McNair et al., 2009), post-percutaneous coronary interventional restenosis (McNair et al., 2010), hyperthyroidism (Caspar-Bell et al., 2016), end-stage renal disease (Prasad et al., 2016), and hypertension (Prasad and Tiwari, 2017). Very little spotlight has been focused on the role of AGE-RAGE axis in the pathophysiology of aortic aneurysm. Understanding the role of AGE and is receptors in the pathogenesis of AA, would provide an insight to chart a novel strategy for prevention, slowing of the progression and regression of the aortic aneurysms. This review addresses the AGE-RAGE axis, AGE-RAGE stress, serum levels AGE, RAGE and sRAGE, interaction of AGE and its receptors, MMPs, inflammatory cytokines, and evidence for involvement of AGE-RAGE stress in the pathogenesis of AA (AAA, TAA).

2. AGE-RAGE axis

AGEs are heterogeneous groups of irreversible adducts that endogenously result from non-enzymatic glycation of proteins, lipids and nucleic acids with reducing sugars (Bucala and Cerami, 1992; Thorpe and Baynes, 2003). The process AGE formation normally occurs at a low rates but is accelerated in hyperglycemia, inflammation, renal failure, Alzheimer's disease and micro- and macrovascular disease (Kalea et al., 2009; Yonekura et al., 2003). AGE has two potentially harmful effects. Firstly crosslinking of AGE with collagen and elastin increases stiffness in the artery (Sell and Monnier, 2012). Secondly, interaction of AGE with RAGE produce reactive oxygen species (ROS) through activation of nicotinamide adenine dinucleotide phosphate (NADPH)-oxidase (Wautier et al., 2001) which activates NF-kB (Gloire et al., 2006). Activated NF-kB activates numerous genes like, TNF-α, IL-1, IL-2, IL-6, IL-8. IL-9 (Reznikov et al., 2004; Stassen et al., 2001). Pro-inflammatory cytokines upregulates NADPH-oxidase (Mohammed et al., 2013) and increase the generation of ROS (Yang et al., 2007). RAGE has two isoforms; cleaved RAGE (cRAGE) and endogenous secretory RAGE (esRAGE). cRAGE is proteolytically cleaved from full length RAGE (Tam et al., 2011), and esRAGE is produced from splicing of full length RAGE mRNA (Yonekura et al., 2003). sRAGE is comprised of both cRAGE and esRAGE. In healthy subjects the serum levels of sRAGE are four to five times higher than the levels of serum cRAGE (Koyama et al., 2005; Prasad et al., 2016). Since the extracellular domain in sRAGE is preserved, the ligand binding capacity is similar to RAGE receptor and hence sRAGE acts as a decoy for RAGE by binding with RAGE ligands (Maillard-Lefebvre et al., 2009; Prasad and Tiwari, 2017). sRAGE binding with ligands does not activate intracellular signaling. sRAGE also is a competitive inhibitor of ligand-RAGE interaction (Wendt et al., 2006). sRAGE acts as cytoprotective agent against adverse effects of AGE- RAGE interaction.

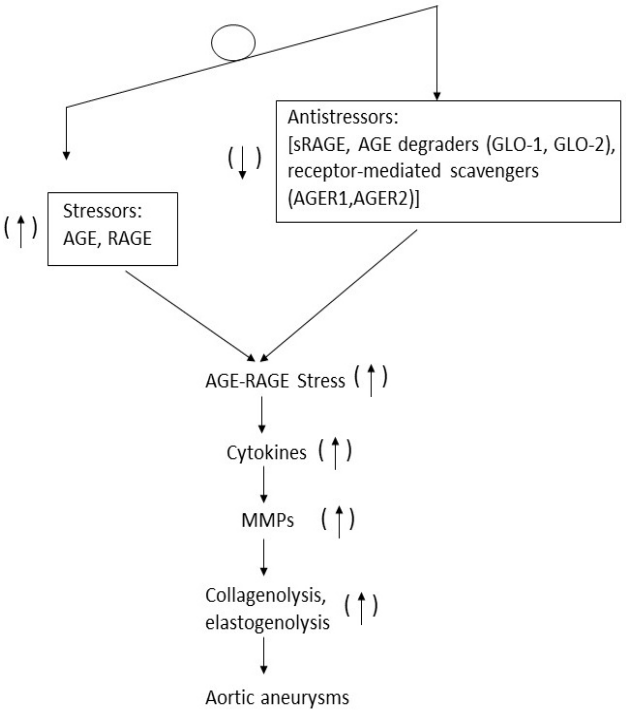

Figure 1. Schematic diagram of involvement of AGE-RAGE stress in the development of aortic aneurysm. AGE, advanced glycation end products; RAGE, receptor for advanced glycation end products; sRAGE, soluble receptor for advanced glycation end products; GLO-1,glyoxalase-1; GLO-2, glyoxalase-2; AGER1, advanced glycation end products receptor 1; AGER 2, advanced glycation end products receptor-2; MMPs, matrix metalloproteinases.; (↑) increase; (↓), decrease.

3. AGE-RAGE stress

The terminology AGE-RAGE stress has been coined by Prasad and Mishra (2018). AGE-RAGE axis is comprised of AGE, RAGE, and sRAGE. AGE and RAGE have been coined as "stressors", while sRAGE, enzymatic degraders of AGE (glyoxalase-1 and glyoxalase-2) and receptor mediated scavenger of AGE [AGE receptor1 (AGER1), and AGE receptor-2 (AGER2)], the agents that lower the blood levels AGE have been coined as "antistressors". AGE-RAGE stress has been defined as a shift in balance between stressors and antistressors in favour of stressors (Prasad and Mishra, 2018). An equation has been developed for the measurement of AGE-RAGE stress by Prasad and Mishra (2018). The ratio of AGE/sRAGE has been put forwarded as a simple and feasible measure of AGE-RAGE stress for clinical practioners. AGE-RAGE stress is risk factor. A high index of AGE-RAGE stress would result in tissue damage and development of disease. AGE-RAGE index is a risk factor and/or a biomarker of disease.

4. Serum, Skin and Aortic Aneurysmal Tissue Levels of AGE in Aortic Aneurysm

The question arises as to if there is an increase in the AGE levels of aortic tissue, skin and serum of patients with aortic aneurysm. The measurement of AGE levels have been made in the aortic tissue, serum and skin of patients with AAA.

4.1 AGE levels in aortic tissue

Zhang et al. (2009) measured the AGE levels in aortic tissue of normal healthy subjects (n = 5) and patients with AAA (n = 8) using immunostaing and observed that AGE levels were significantly higher in aorta of patients with AAA than in aorta of healthy subjects. Expression of AGE measured by ELISA kit for AGE was 2.7-folds higher in aorta of patients with AAA than in aorta of normal subjects.

Koole et al. (2017) reported that levels of pentosidine were higher in the arterial wall of AAA patients with diabetics compared with the aorta of nondiabetics (9.4; range 5.0-13.5) vs. 6.6; range 2.5-9.6) pmole/umol lysine; $P = 0.02$. These investigators also reported that non- crossd-linked AGE [carboxymethyllysine (CML), carboxyethyllysine (CEL)] were similar in AAA patients with diabetes and without diabetes, while the levels of cross-linked AGE (pentosidine) were higher in AAA patients with diabetes compared to nondiabetics. They also observed that pentosidine levels of aortic tissue were significantly higher in diabetic aorta than in non-diabetic aorta. The levels of CML and CEL in aortic tissue were lower to a similar extent in aortic tissue compared to control non-diabetic and diabetic subjects. Although the reduction in pentosidine levels in AAA with or without diabetes were similar as compared to control and diabetic aorta, the reduction of pentosidine in non- diabetic AAA was more than in AAA with diabetes. They concluded that the levels of pentosidine in aortic tissue were more in AAA patients with diabetes than in non-diabetic patients.

4.2 Serum levels of AGE

Measurement of the serum levels of CML in community living men with diabetes of age group between 65 and 79 years were made by Norman et al. (2009). The patient population comprised of diabetic men with AAA (n = 27) and non-diabetic men (n = 67). The controls were age-matched diabetic men (n = 69) and non- diabetic men without AAA (n = 70).These investigators reported that the levels of serum CML were lower in diabetic men with AAA than those without AAA (6626 ± 1352 vs.7712 ± 1518 nmol/ml lysine; $P = 0.001$). They also reported that the serum levels of CML were negatively associated with AAA ($P = 0.016$). However the levels of serum CML were not significantly different between non- diabetic patients with or without AAA (6917 ± 1361 vs. 6749 ± 1615 nmol/mole lysine). These investigators observed that anatomical and physiological differences were consistent with negative association between diabetes and AAA which may be due to differences in vascular matrix (Norman et al., 2007).

Serum levels of AGE were measured in two sets of patients: control and patients with TAA (Prasad et al., 2016). The serum AGE levels were 6.3-folds higher in TAA patients compared to controls (20.06 ± 3.69 vs. 2.93 ± 0.97 ug/ml).

In a cross sectional multicenter study measurements of serum, urine and skin levels of AGE have been proposed in 120 AAA patients with or without diabetes (30 in each group) (de Vos et al., 2017). The data are not available as yet.

4.3 AGE levels in skin

Skin autofluoresence (SAF) were measured in a case control study of 248 patients with AAA and 124 control subjects without AAA or peripheral artery disease matched for age and diabetes by Boersema et al. (2017). SAF is a non-invasive technique for measurement of AGE in skin (Boersema et al., 2017). Skin collagen turn over is estimated to be 15 years and skin AGE and SAF represent a long-term metabolic memory (Verzijl et al., 2000). SAF levels correlated with AGE concentrations in venous bypass graft material (Hofmann et al., 2013). SAF levels were higher in patients with AAA than control subjects (2.89 ± 0.04 vs. 2.68 ± 0.06; $P = 0.003$) arbitrary unit (Boersema et al., 2017). Using multivariate regression analysis, they also reported that age, current smoking, hypertension and peripheral artery disease (PAD) were determinants of SAF in AAA, while sex, diabetes, body mass index, lipid lowering drugs, anticoagulant therapy, aortic diameter, and history of coronary artery disease (CAD) or cardiovascular disease (CVD) were not. These investigators also reported that in a crude model of logistic regression, there was an association between SAF and AAA. This association remained unaltered after correction of cardiovascular morbidity but was lost after correction for sex, current smoking, hypertension and use of lipid lowering medications.

5. Levels of RAGE Expression in Aortic Tissue of Aortic Aneurysm

The levels of RAGE expression in human AAA tissue were higher compared to that in tissue from normal aorta (Zhang et al., 2009). These investigators also observed that there was a significant upregulation of RAGE expression in aortic tissue of mouse model of AAA as compared to aortic tissue of normal mouse.

6. Serum sRAGE and esRAGE levels in Patients with Aortic Aneurysm

Levels of serum sRAGE and esRAGE have been measured in control subjects (n = 17) and in patients with TAA (n = 20) (Prasad et al., 2016). The serum levels of sRAGE were significantly lower in TAA patients compared to controls. The levels of esRAGE were not significantly different between control subjects and TAA patients.

The serum levels of sRAGE were measured in 80 patients with AAA and 80age-matched healthy control subjects (Yao et al., 2015). The serum levels of sRAGE in patients with AAA were 0.989-fold lower than in control (918.58 ± 152.36 vs. 625.39 ± 121.55 pg/ml; $P = 0.035$). They reported that the serum levels of sRAGE were significantly (1.45-folds lower in patients with RAGE 82GS + 82SS genotype than those with RAGE 82 GG genotype (852.25 ± 33.66 vs. 586.0 ± 108.23 pg/ml of serum). They also reported that there was a significant reduction in concentration of serum sRAGE in AAA male patients with RAGE genotype 82GS + 82SS than the controls RAGE 82GG genotype (756.18 ± 117.15 vs. 481.26 ± 128.88 pg/ml serum; $P = 0.036$) and in patients with cigarette smoking (665.86 ± 109.33 vs. 453.82 ± 115.72 pg/ml serum; $P = 0.012$) with variant RAGE genotype 82GG and 82GS. These data of Yao et al. (2015) support that there is a significant association between RAGE 82GS polymorphism and the risk of developing AAA.

7. AGE-RAGE stress (AGE/sRAGE) in Patients with TAA

The AGE/sRAGE ratio were measured in control subjects and TAA patients by Prasad et al. (2016) (Fig. 1). The ratio of AGE/sRAGE and AGE/esRAGE were respectively 10.4-folds and

8.18-folds higher in TAA patients than in controls. In summary AGE-RAGE stressis higher in patients with TAA compared to controls. There is no available data for AGE-RAGE stress in AAA.

8. Serum Levels of Cytokines and MMPs in AAA and TAA

Serum levels of cytokines have been reported to be elevated in patients with AAA (Jones et al., 2001; Juvonen et al., 1997; Rohde et al., 1999) and TAA (Prasad et al., 2016). Serum levels of MMPs are also elevated in patients with AAA (McMillan and Pearce, 1999; Nordon et al., 2009) and TAA (Prasad et al., 2016). The following sections deal with the levels of cytokines and MMPs in AAA and TAA, and their relationship with AGE, RAGE, sRAGE and AGE-RAGE stress.

8.1 Serum levels of cytokines in AAA and TAA

The serum levels of IL-1β, IL-6, TNF-α, and IFN-Y are elevated in patients with AAA as compared to control subjects (Jones et al., 2001; Juvonen et al., 1997). The serum levels of IL-1β, IL-2, IL-6 and TNF-α were respectively 3.49-, 22.38-, 10.65-, and 3.35-folds higher in patients with TAA as compared with control subjects (Prasad et al., 2016). The data suggest that the serum levels of cytokines (IL-1β, IL-2, IL-6, TNF-α and IFN-Y) are elevated both in AAA and TAA.

8.2 Levels of MMPs in Serum and Aortic Tissue of Patients with AAA and TAA

The serum levels of MMP-2 and MMP-3 were respectively 29.61% and 142.1% higher in TAA patients compared to control subjects (Prasad et al., 2016). Serum levels of MMP-2, MMP-3, MMP-8 and MMP-9 were high in patients with AAA (McMillan and Pearce, 1999; Watanabe et al., 2006) and in TAA (Prasad et al., 2016; Símová et al., 2013).

The activity of MMP-9 in aortic tissue was significantly higher in patients with AAA than in aortic tissue of control subjects (Zhang et al., 2009).These investigators also reported that the activity of MMP-9 was higher in mouse model of AAA compared to RAGE knockout mice where there was no aortic aneurysm.

9. Correlation of AGE, RAGE, sRAGE, and AGE-RAGE Stress with Cytokines in Patients with AA

Prasad et al. (2016) have shown that serum levels of AGE was positively correlated with serum IL-1β and IL-6. There was a negative correlation of sRAGE with IL-1β, IL-2, and IL-6 but significant only between sRAGE and IL-6 in patients with TAA. There was a tendency for positive correlation between AGE and IL-2 and between AGE and TNF-α, but the correlation was not significant. These authors did not find any correlation between sRAGE and TNF-α. There was a positive correlation of AGE-RAGE stress with IL-1β, IL-2, IL-6 and TNF-α but the correlation was significant only with IL-2.The correlation between tissue RAGE and cytokines has not been reported till now.

10. Correlation of AGE, RAGE, sRAGE, and AGE- RAGE Stress with MMPs

Serum levels of AGE are positively correlated with the serum levels of MMP-2 in patients with TAA (Prasad et al., 2016). These investigators also reported that AGE- RAGE stress was positively correlated with MMP-2 and MMP-3 in patients with TAA. Serum sRAGE on the other hand was negatively correlated with MMP-3. Zhang et al. (2009) investigated if there is an association of AGE and RAGE with MMP-9.

An investigation was made by Zhang et al. (2009) to determine if there is any association of AGE and RAGE with MMP-9. In this study they stimulated vascular smooth muscle cells or macrophage cell line with increasing amounts of AGE and observed that AGE increased the MMP-9 activity in macrophage in a concentration-dependent manner without significantly affecting the activity of MMP-2 that has been implicated in the development of AA. AGE did not increase the enzymatic activity of MMP-2 or MMP-9 in vascular smooth muscle cells. These investigators demonstrated that the effect of AGE on MMP- 9 is due to interaction of AGE with RAGE because anti-RAGE blocking antibody or sRAGE significantly reduced AGE-induced activity of MMP-9.

11. Correlation of Cytokines with MMPs

There was a positive correlation of IL-1β, IL-2, IL-6 and TNF-α with MMP-2 but the correlation was significant only between IL-1β and MMP-2 in patients with TAA (Prasad et al., 2016). These investigators also reported that the levels of IL-1β, IL-2 and TNF-α, were correlated with MMP-3 but the correlation was significant only between IL-1β and MMP-3. In summary the data suggest that cytokines have a positive correlation with MMPs.

12. Mechanisms by which AGE-RAGE Stress induces Aortic Aneurysms

As described earlier in section 3, AGE-RAGE stress involves AGE, RAGE, and sRAGE. The roles of AGE, RAGE, sRAGE and AGE/sRAGE in pathogenesis of AAs are described below.

12.1 AGE

The data (sections 4-7) show that the levels of AGE in serum (Boersema et al., 2017; Koole et al., 2017; Norman et al., 2007, 2009; Prasad et al., 2016; Zhang et al., 2009), and aortic tissue, RAGE (Zhang et al., 2009) in aortic tissue are increased, while the serum levels of sRAGE and esRAGE (Prasad et al., 2016; Yao et al., 2015) are reduced in patients with AAA and TAA as compared to controls The AGE/sRAGE ratio (Prasad et al., 2016), and AGE/esRAGE ratio (Prasad et al., 2016) are high in patients with TAA as compared to control subjects. The levels of IL-1β, IL-2, IL-6, IL-9, TNF-α, and IFN-Y in serum are elevated in patients with AAA and TAA as compared to controls (Jones et al., 2001; Juvonen et al., 1997; Prasad et al., 2016; Rohde et al., 1999). The serum levels of MMP-2, MMP-3, MMP-8, and MMP-9 are elevated in patients with TAA (Prasad et al., 2016; Símová et al., 2013) and AAA (McMillan and Pearce, 1999; Watanabe et al., 2006).

As described earlier in section 2, AGE-RAGE intraction increases the expression of numerous cytokines (Reznikov et al., 2004; Stassen et al., 2001). Cytokines (IL-1β, IL-2, IL-6, IL-9, TNF-α) increase the expression of MMPs (MMP-2, MMP-3, MMP-9) (Edsparr et al., 2010; Kossakowska et al., 1999; Kusano et al., 1998; Mountain et al., 2007; Wong et al., 2001). MMPs have elastolytic and collagenolytic activities (Van Doren, 2015) and have been implicated in the development of aortic aneurysms (Kotze and Ahmad, 2011; Theruvath et al., 2012).

The increases of cytokines levels with AGE-RAGE interaction would increase the levels of MMPs which in turn would affect the collagen and elastin tissue, culminating in the development of AA. If this is the case then the serum levels of AGE and AGE/sRAGE will be positively correlated with cytokines and MMPs, while sRAGE would have negative correlation with cytokines and MMPs. Also cytokines would have positive correlation with MMPs. It has been reported that AGE has positive correlation with IL-1β and IL-6 but not with IL-2 and TNF-α in patients with TAA (Prasad et al., 2016). These investigators also reported that there was a positive correlation of AGE/sRAGE with IL-1β, and IL-6 but the correlation was not significant. They also showed that here was a negative correlation of sRAGE with IL-1β, IL-2, and IL-6 but the correlation was not significant. Prasad et al. (2016) reported that AGE/sRAGE was positively correlated with MMP-2 and MMP-3. sRAGE was negatively correlated with MMP-3 but was not significant (Prasad et al., 2016). IL-1β has been reported to be positively correlated with MMP-2 and MMP-3 (Prasad et al., 2016). There was a was positive correlation of IL-2 with MMP-2 and MMP-3, but the correlation was not significant. IL-6 tended to correlate positively with MMP-2, but the correlation was not significant.

There are evidence that AGE increases the levels of MMP-9. AGE has been shown to induce the production of MMP-9 in murine macrophage cell line RAW 264.7 in a dose-dependent manner (Zhang et al., 2011). In other study, Zhang et al. (2009) assessed the relationship of AGE-RAGE axis with production of MMP-9.In this study the vascular smooth muscle cells or macrophage cell line was activated with increasing amount of AGE. They observed that there is a AGE- concentration-dependent elevation of the activity of MMP-9, however other MMPs which are associated with development of aortic aneurysms were not affected. There was no increase in the activity of MMP-2 and MMP-9 with AGE in vascular smooth muscle cells. A significant increase in the levels of MMP-9 mRNA in AGE-stimulated macrophage was reported by Zhang et al. (2009), and this effect of AGE was significantly reduced with RAGE blocking antibody or sRAGE.

AGE may also increase the levels of MMPs in aortic tissue through glycation or cross-linking with serum albumin and collagen. Glycated bovine serum albumin and glycated monomer collagen have been shown to increase the secretion of MMP-9 in THP1 cells (Golledge et al., 2008). However, they showed that glycated collagen lattices and cross-linked collagen lattices reduce the secretion of MMP-2 and MMP-9 in THP1 cells and peripheral blood mononuclear cells.

12.2 RAGE

If RAGE is involved in the pathogenesis of AAs, then deletion of RAGE would reduce the levels of MMPs and prevent the development of AAs. Myloid RAGE is involved in aneurysmal degeneration in mouse model of AAAs (Raman et al., 2016). In RAGE knockout mice, the inflammation of the aortic wall and proteolytic activity were reduced and that would have preserved elastin.

In experimental studies a complex role of AGE and RAGE was observed in angiotensin II-induced AAA model using Apo -1- RAGE -1- mice. Deficiency in RAGE reduced the incidence of AAA and this effect was associated with reduction in MMP-9 activity and cellularity of adventitia of aorta (Zhang et al., 2009). These investigators also demonstrated that stimulation of murine macrophage cell line RAW264.7 with AGE increased MMP-9 gene expression and activity.

In transgenic mice overexpression of the human RAGE ligand (S100A12) exhibited progressive dilatation of aorta with elastin fiber disruption, fibrosis and loss of vascular smooth muscle cells in the medial layer of aorta (Hofmann et al., 2010). These changes were associated with increases in the expression of MMP-2.

It has been shown that there is an association between RAGE gene polymorphism and AAA, and that 82 S allele of RAGE is a risk factor for AAA (Yao et al., 2015).

12.3 sRAGE

As mentioned earlier sRAGE has protective effects against adverse effects of interaction of AGE with RAGE. AGE increases the activity of MMP-9 in microphages and sRAGE significantly blocks this response of AGE on MMP-9 (Zhang et al., 2009), suggesting that sRAGE would be effective in the prevention, slowing of progression and regression of AA. In summary the elevated levels of AGE, RAGE, AGE-RAGE stress and low levels of sRAGE would increase the levels of cytokines that would increase the levels of MMPs resulting in the development of AAA and TAA (Fig. 1). This hypothesis had been suggested previously by Prasad et al. (2016).

13. Treatment Modalities for Aortic Aneurysm (AA)

If AGE-RAGE axis is involved in the pathogenesis of AA, the treatment strategy for AA should be directed towards reduction of AGE levels, suppression of RAGE expression, blocking of AGE binding to RAGE and elevation of sRAGE. Additionally antioxidants would be helpful in patients with AA. These strategies have been described in detail for treatment of other AGE-RAGE stress-induced diseases (Prasad, 2019a,b; Prasad and Tiwari, 2017). The details, therefore, will not be described here. Only summary will be provided.

13.1 Lowering of AGE levels

AGE levels can be reduced by reduction in dietary consumption of AGE by lowering consumption of diet with high content of AGE that include red meat, cheese,cream, butter and animal fat. Cooking at high temperature in dry heat (frying, broiling, grilling and roasting) should be avoided because it increases in AGE formation. Cigarette smoking should should be discontued because it increases the serum levels of AGE. Reduction in the levels of AGE can be achieved by prevention of AGE formation by using certain vitamins (benfotiamine, vitamins B_6, C, D and E), acidic ingradients (Lemon, Vinegar). Degradation of AGE by using AGE degrading enzymes and receptor-mediated degraders of AGE would reduce the levels of levels of AGE.

13.2 RAGE antagonists

RAGE antagonists are of three types; suppression of RAGE expression, blocking of RAGE binding to AGE, and sRAGE. Certain drugs (statins, angiotensin II, receptor blocker, antidiabetic drugs, calcium channel blocker and curcumin) downregulate the expression of RAGE. There are some new drug (Azeliragon and TTP4000) which can prevent the binding of AGE with RAGE.

sRAGE competes with RAGE to bind with AGE and hence it blocks the effects of AGE-RAGE binding.

13.3 Elevation of sRAGE levels

There are certain drugs (statins, angiotensin converting enzyme inhibitors, antidiabetic drugs, and vitamin D) that elevate the levels of sRAGE. Exogenously administered sRAGE would also elevate the serum levels of sRAGE.

13.4 Antioxidants

Antioxidats (vitamins C, D, and E; and melatonin) have been reported to be beneficial in Alzheimer's patients. It is to note that none of the therapeutic measures have been tried in patients with AAs. Studies should be conducted to evaluate the efficacy of the above measures in the treatment of AAs.

14. Summary and Conclusion

The data show that 1). AGE levels in aortic tissue, skin and serum of patients with aortic aneurysms (AAA, TAA) are elevated; 2). RAGE levels in aortic tissue are elevated in abdominal aortic aneurysms; 3). AGE-RAGE stress is elevated in TAA patients; and 4). Levels of serum sRAGE are reduced in patients with AAA and TAA; 5). The serum levels of cytokines and MMPs are elevated in AAA and TAA; 6). There is a positive correlation of serum levels of AGE and AGE- RAGE stress with cytokines and MMPs, while serum levels of sRAGE are negatively correlated with cytokines and MMPs. Measures have been described for the treatment of AAs. In conclusion the cumulated data suggest that elevated levels AGE, RAGE and AGE-RAGE stress, and reduced levels of sRAGE increase the levels of cytokines which in turn increase the levels of MMPs resulting in the development of AAA and TAA. Novel potential therapeutic targets have been described.

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Conflict of interest

No conflict of interest.

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