Role of Advanced Glycation Endproduct (AGE)-Receptor for Advanced Glycation Endproduct (RAGE) Axis in Cardiovascular Disease and Its Therapeutic Intervention

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Despite the early loss of glycemic differences between the original intensive therapy group and conventional treatment in the DCCT/EDIC and UKPDS 80 trials, a continued reduction in microvascular risk and risk reductions for emergency myocardial infarction and all-cause death were observed 10–30 years after the end of these trials. These observations demonstrated that so-called “metabolic memory” could cause chronic abnormalities in diabetic vessels that are not easily reversed, even by subsequent improvement in blood glucose levels, thus suggesting a long-term beneficial influence of early metabolic control; that is, legacy effects on the risk of vascular complications and death in patients with both type 1 and type 2 diabetes. Formation and accumulation of advanced glycation endproducts (AGEs) are known to progress at an accelerated rate under diabetes. Furthermore, AGEs are hardly degraded and remain for a long time in diabetic vessels even after glycemic control is improved. Therefore, AGEs could explain why former cumulative diabetic exposure could contribute to current progression of vascular complications in diabetes. Here, the clinical utility of measurement of serum and tissue accumulation levels of AGEs for evaluating the prevalence and severity of numerous types of cardiovascular disease is reviewed and novel therapeutic strategies that could target the AGE-RAGE axis in CVD are discussed.

Key Words: Advanced glycation endproducts (AGEs); Cardiovascular disease; Diabetes; Receptor for advanced glycation endproduct (RAGE); Skin autofluorescence

Monosaccharides, such as glucose, fructose and glyceraldehyde, can react non-enzymatically with the amino groups of proteins, nucleic acids, and lipids to form reversible Schiff bases, and then Amadori products. Over the course of days to weeks, these early products undergo further complex reactions, including rearrangement, dehydration and condensation to constitute a heterogeneous group of irreversible adducts termed “advanced glycation endproducts” (AGEs) (Figure 1). Nonenzymatic glycation of macromolecules alter their structural integrity and physiological function, the process of which progresses under aging, diabetic or inflammatory conditions. Moreover, AGEs are recognized by a cell surface receptor (RAGE) that belongs to the immunoglobulin superfamily, which could cause oxidative stress and resultantly evoke inflammatory and fibrotic reactions in numerous types of cells and tissues, thereby playing a crucial role in the development and progression of aging- and/or diabetes-associated disorders such as atherosclerotic cardiovascular disease (CVD) (Figure 2).

There is accumulating evidence to show the pathophysiological involvement of “metabolic memory” in vascular complications in diabetes. Indeed, although intensive management of blood glucose for 6.5–10 years did not significantly reduce the risk of CVD or death in both type 1 and 2 diabetic patients, the 10–30-year follow-up studies of the Diabetes Control and Complications Trial (DCCT) and United Kingdom Prospective Diabetes Study (UKPDS) revealed that the risk of CVD and all-cause death were significantly lower in the former intensive therapy group compared with conventional therapy, associated with continued risk reduction of microvascular complications. Moreover, in the Veterans Affairs Diabetes Trial, risk reduction of emergency CVD in diabetic patients originally assigned to intensive therapy was observed over a 10-year follow-up. These observations indicate that past cumulative diabetic exposure can persistently cause chronic abnormalities in diabetic vessels, kidneys, and hearts that are not easily reversed, even by subsequent, relatively good glycemic control.

AGEs are hardly degraded and remain for a long time in various types of diabetic tissues. Engagement of RAGE with AGEs can further promote the formation and accumulation of AGEs and induce RAGE expression via oxidative stress, thereby creating a positive feedback loop in an AGE-RAGE axis (Figure 2). In addition, skin levels of AGE-modified collagen at the close of the DCCT were reported to correlate with the progression of carotid artery intima-media thickness (IMT) during the follow-up period. These findings suggested that activation of the AGE-RAGE axis may partly explain the phenomenon of former diabetic exposure contributing to current progression.

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AGEs and CVD

Figure 1. Pathway of formation of advanced glycation endproducts (AGEs).

Figure 2. Role of AGE-RAGE axis in aging-related disorders. AGEs, advanced glycation endproducts; CVD, cardiovascular disease; RAGE, receptor for AGEs.

of vascular complications in diabetes. Therefore, the clinical utility of measurement of serum and tissue accumulation levels of AGEs for evaluating the prevalence and severity of various kinds of CVD is reviewed and novel therapeutic strategies that could target the AGE-RAGE axis in CVD are discussed.

**Tissue Levels of AGEs and CVD**

Tissue accumulation of AGEs can be non-invasively measured as skin autofluorescence (SAF) by an AGE-Reader (Diagnoptics, Groningen, Netherlands). SAF is defined as the ratio of average autofluorescence over the entire 420–600-nm emission spectrum to that over 300–420 nm, which correlates with pentosidine and Nε-(carboxymethyl)lysine (CML), well-characterized fluorescent and non-fluorescent AGEs, respectively, in the skin. Although signals from skin fluorophores, such as NAD(P)H and FAD can affect the SAF values, skin AGEs have been shown to contribute 76% of the variance in the SAF signal.
from the AGE-Reader.26,27

Cross-linking modification of matrix proteins, such as collagen and elastin by AGEs, is involved in arterial and myocardial stiffness, which are associated with increased risk of CVD.5,25 SAF is independently associated with arterial stiffness evaluated by pulse wave velocity in type 1 diabetic patients without a history of CVD and in subjects with endstage renal disease (ESRD).28,29 Furthermore, SAF correlates with diastolic dysfunction and/or reduced aerobic capacity in diabetic patients with heart failure and in subjects on dialysis.30

SAF is independently associated with carotid IMT, a marker of atherosclerosis in non-diabetic patients without clinically manifest CVD.31 In addition, SAF significantly correlates with carotid IMT, high-sensitivity C-reactive protein, and plasma pentosidine, and is associated with the presence of CVD in hemodialysis subjects.32 Moreover, SAF is associated with low levels of circulating endothelial progenitor cells in patients with ESRD, suggesting the involvement of AGEs in impaired endothelial cell repair.33 SAF is also independently associated with macrovascular complications in patients with type 2 diabetes.34–36

SAF is significantly associated with coronary artery calcium score in patients with chronic kidney disease.37 Optical coherence tomography revealed that high SAF is associated with plaque vulnerability, such as thin-cap fibroatheroma, calcified plaques, and ruptured plaques in patients with CVD.38

SAF can predict future cardiovascular events in patients with ST-elevation myocardial infarction,39 and is also an independent predictor of graft loss in renal transplant recipients.40 SAF is significantly higher in patients with peripheral artery disease, which predicts future limb amputation, cardiovascular events and 5-year mortality independently of traditional risk factors.41,42 SAF is also higher in patients with chronic cerebral infarction or silent brain infarction compared with controls.43

SAF independently predicts overall and cardiovascular mortality risks in Caucasian patients on hemodialysis.44 In addition, SAF is associated with the prevalence of CVD and is an independent predictor of CVD death in Japanese subjects on hemodialysis.45,46 High SAF levels correlate with an increased risk of all-cause death in peritoneal dialysis patients; SAF values >3.61 arbitrary units predict death in these subjects.47,48 A systematic review revealed that SAF is significantly associated with a higher pooled risk estimate for death from cardiovascular causes and total mortality in high-risk patients such as those with ESRD.49 In a median 4-year follow-up study of more than 70,000 participants without diabetes or CVD, SAF was shown to predict the development of type 2 diabetes, CVD, and death, independently of classical risk factors.50

Accumulation of CML increases in the atrial appendage of patients with atrial fibrillation, which is associated with severity of fibrosis in both diabetic and non-diabetic subjects.51–53

Circulating Levels of AGEs and CVD

Serum levels of AGE levels correlate with the soluble form of RAGE, a marker that can reflect tissue RAGE expression in both non-diabetic and diabetic subjects.54,55 Furthermore, circulating levels of AGEs were independently associated with low-density lipoprotein cholesterol and thrombotic markers, such as plasminogen activator inhibitor-1 and fibrinogen, in a general population.56,57 In addition, AGEs levels correlate with inflammtory and/or endothelial cell damage biomarkers, including monocyte chemoattractant protein-1, soluble form of vascular cell adhesion molecule-1, and asymmetric dimethylarginine.58,59,60 AGEs not only

Figure 3. DNA-aptamers directed against advanced glycation endproducts (AGEs) and their receptor (RAGE).
correlate with vascular inflammation and endothelial dysfunction in high-risk patients for CVD.\(^{68-70}\) but are also associated with reduced number and migratory activity of endothelial progenitor cells.\(^{70}\) Serum levels of AGEs are reported to predict atherosclerotic plaque progression in patients with acute coronary syndrome (ACS).\(^{71}\)

Serum levels of AGEs are elevated in patients with non-alcoholic steatohepatitis, and associated with insulin resistance irrespective of the presence or absence of non-alcoholic steatohepatitis.\(^{72-74}\) Indeed, AGEs positively correlate with serum levels of pigment epithelium-derived factor and dipeptidyl peptidase-4, markers of insulin resistance\(^{75-76}\) and inversely associated with adiponectin values.\(^{72}\) Cirulating levels of AGEs are independently associated with inflammation in the visceral and subcutaneous adipose tissues.\(^{77}\)

Cirulating levels of AGEs, such as CML and methylglyoxal-derived hydroxymidazalone, are reported to predict total mortality and/or CVD death in both type 1 and type 2 diabetic patients, subjects on hemodialysis, non-diabetic subjects, and patients with ACS.\(^{78-83}\) Increased levels of CML also predicted CVD death among older community-dwelling women.\(^{84}\) Moreover, non-diabetic older adults with plasma CML in the highest tertile had greater all-cause and CVD mortality compared with those in the lower 2 tertiles.\(^{85}\)

Cirulating levels of CML or pentosidine have also been reported to be an independent prognostic factor of heart failure.\(^{86-87}\)

**Therapeutic Intervention of the AGE-RAGE Axis**

Diet and smoking are major environmental sources of pro-oxidative and pro-inflammatory AGEs.\(^ {88-90}\) Fat-rich foods cooked at high temperature or ultraprocessed meat-derived products contain greater amounts of AGEs.\(^ {91}\) On the other hand, foods prepared at lower temperature with more moisture, especially under acid conditions contain less AGEs.\(^ {88-90}\) Because 7% of exogenously derived AGEs is considered to remain in the body,\(^ {92-93}\) restriction of consumption of dietary AGEs is a novel therapeutic target that could block the AGE-RAGE axis.\(^ {88-90,94-99}\) Indeed, a low-AGE diet improved renal function in overweight and obese individuals, which was associated with a reduction in inflammatory biomarkers, including serum levels of AGEs.\(^ {95-96}\) In addition, restriction of dietary AGEs resulted in a significant decrease in the serum levels of C-reactive protein and plasminogen activator inhibitor-1 in patients with ESRD, which may contribute to cardiovascular protection.\(^ {97}\) A recent meta-analysis of randomized controlled trials revealed that consumption of a low-AGE diet decreased the levels of total cholesterol, circulating AGEs, and inflammatory and oxidative stress biomarkers, such as tumor necrosis factor-α, soluble vascular cell adhesion molecule-1, and 8-isoprostane total, in patients with and without type 2 diabetes.\(^ {98}\)

Aptamers are short, single-stranded RNA or DNA oligonucleotides that can bind to various proteins, peptides, and viruses with high specificity and affinity.\(^ {99-101}\) DNA-aptamers directed against AGEs and RAGE (AGE-aptamers and RAGE-aptamers) that attenuate the interaction of AGEs with RAGE in vitro have been recently developed (Figure 3).\(^ {102}\) The AGE-aptamer significantly attenuates neointimal formation after balloon angioplasty in rats through a reduction of platelet-derived growth factor-BB via suppression of the AGE-RAGE oxidative stress axis.\(^ {103}\) Moreover, AGE-aptamers inhibited insulin resistance and adipose tissue remodeling in fructose-fed rats, progression of diabetic nephropathy in type 2 diabetic mice, development of diabetic retinopathy in type 1 diabetic rats, and growth of malignant melanoma in nude mice.\(^ {104-107}\) Furthermore, RAGE-aptamers promoted regression of experimental diabetic nephropathy in type 1 diabetic animals, attenuated melanoma growth and metastasis in nude mice, and ameliorated renal injury in hypertensive mice.\(^ {108-109}\) These findings suggest that blockade of the AGE-RAGE axis by AGE- or RAGE-aptamers may be a therapeutic target for CVD.

**Perspectives**

A growing body of evidence suggests the clinical utility of measuring tissue and circulating levels of AGEs for evaluating the severity and prognosis of various types of CVD. A recent pilot study revealed that switching dipeptidyl peptidase-4 inhibitors to an inhibitor of sodium-glucose cotransporter 2 ameliorated arterial stiffness in type 2 diabetic patients, which was associated with a reduction in the serum levels of AGEs.\(^ {110}\) Further longitudinal study is needed to clarify whether a reduction in the burden of AGEs by sodium-glucose cotransporter 2 inhibitors or consumption of a low-AGE diet could contribute to CVD protection in patients with type 2 diabetes.

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