Soluble Receptor of Advanced Glycated Endproducts Is Associated With Plaque Vulnerability in Patients With Acute Myocardial Infarction

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Background: The roles of soluble and endogenous secretory receptors for advanced glycation endproducts (sRAGE and esRAGE, respectively) in plaque vulnerability are unknown in patients with acute myocardial infarction (AMI).

Methods and Results: We enrolled 54 patients with AMI (27 patients had type 2 diabetes mellitus [DM]) who had undergone primary percutaneous coronary intervention, and 54 controls who were matched for age, gender and the presence of DM. Plasma levels of s/esRAGE and matrix metalloproteinase (MMP)-9 were measured at the time of coronary angiography. There were no significant differences in the baseline characteristics of the AMI and control groups, except for the C-reactive protein levels (CRP: 14.1 ± 14.2 mg/L vs. 3.7 ± 5.2 mg/L, $P < 0.001$). The plasma levels of MMP-9 (28.6 ± 21.4 vs. 14.3 ± 8.5 ng/ml, $P < 0.001$) and sRAGE (0.61 ± 0.28 vs. 0.41 ± 0.17 ng/ml, $P < 0.001$) were higher in the AMI group than in the controls. In multivariate logistic regression analysis, the plasma levels of MMP-9 and sRAGE above the median (odds ratio [OR], 2.39; 95% confidence interval [CI], 1.02–5.58; $P = 0.044$; OR, 2.47; 95%CI, 1.05–5.80; $P = 0.039$, respectively) were independent predictors of AMI, as well as being a current smoker (OR, 2.98; 95%CI, 1.18–7.55; $P = 0.021$) and CRP ≥ 3.0 mg/L (OR, 3.08; 95%CI, 1.25–7.59; $P = 0.015$).

Conclusions: An elevated plasma level of sRAGE might be independently associated with plaque vulnerability, as well as MMP-9, in patients with AMI. (*Circ J* 2011; **75**: 1685–1690)

Key Words: Acute myocardial infarction; Matrix metalloproteinase-9; Plaque vulnerability; Soluble receptor for advanced glycation endproducts

Plaque rupture is the main cause of acute myocardial infarction (AMI).^{1,2} The immediate site of the rupture is always marked by an inflammatory process, which suggests that inflammation plays a role in destabilizing the fibrous cap and thus in enhancing the risk of coronary thrombosis.³ Previous reports are that increased macrophage density and/or activation in the atherosclerotic plaque may induce collagen breakdown in the fibrous cap by secreting matrix metalloproteinases (MMPs), and possibly other proteases, thus contributing to the plaque's vulnerability to rupture.^{4–6}

Diabetes mellitus (DM) is associated with a higher incidence of AMI. The relative risk of incident of AMI is increased 2–3-fold in those with type 2 DM, and the risk of death is increased 2-fold, independent of other risk factors of coronary artery disease (CAD).⁷ The possible mechanism involves enhanced cellular oxidant stress by the interaction of advanced glycation endproducts (AGEs) with their receptors (RAGE), which may quench nitric oxide through the generation of oxygen free radicals, leading to impaired endothelial function, leukocyte adhesion, platelet aggregation,

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Table 1. Baseline Characteristics of the AMI Group and Controls at the Time of the Coronary Angiography

	AMI (n=54)	Control (n=54)	P value
Clinical variables			
Age, years	64.2±13.1	62.2±12.0	0.396
Male sex, n (%)	27 (50.0)	27 (50.0)	1.000
BMI, kg/m ²	23.8±2.6	24.9±3.6	0.084
Hypertension, n (%)	28 (51.9)	29 (53.7)	0.847
Diabetes mellitus, n (%)	27 (50.0)	27 (50.0)	1.000
Hyperlipidemia, n (%)	11 (20.4)	7 (13.0)	0.302
Current smoking, n (%)	24 (44.4)	15 (27.8)	0.071
Laboratory variables			
Hemoglobin, g/dl	13.8±1.7	13.2±1.9	0.124
Cr, mg/dl	1.01±0.36	0.99±0.42	0.860
TC, mg/dl	177.5±48.1	178.4±42.2	0.923
TG, mg/dl	139.5±83.0	154.1±103.2	0.422
HDL, mg/dl	43.3±9.3	44.1±11.8	0.708
LDL, mg/dl	106.0±42.3	107.0±33.0	0.900
HbA _{1c} , %	6.9±1.6	7.1±1.9	0.643
CRP, mg/L	14.1±14.2	3.7±5.2	<0.001
Medications, n (%)			
Aspirin	15 (27.8)	17 (31.5)	0.673
β-blocker	8 (14.8)	9 (16.7)	0.792
ACEI/ARB	16 (29.6)	18 (33.3)	0.679
CCB	21 (38.9)	14 (25.9)	0.150
Statin	7 (13.0)	6 (11.1)	0.767
OHA	23 (42.6)	22 (40.7)	0.845
Insulin	6 (11.1)	4 (7.4)	0.507

AMI, acute myocardial infarction; BMI, body mass index; Cr, creatinine; TC, total cholesterol; TG, triglycerides; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HbA_{1c}, glycosylated hemoglobin; CRP, C-reactive protein; ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker; CCB, calcium-channel blocker; OHA, oral hypoglycemic agent.

and cytokine expression, resulting in macrophage infiltration at the site of atherosclerotic plaques and increased plaque vulnerability.^{8,9}

Soluble forms of RAGE appear in the plasma as spliced variants (endogenous secretory receptor for AGE [esRAGE]) leaking through the transmembrane and cytosolic domain,¹⁰ and as a proteolytically cleaved form of RAGE (sRAGE), which is most probably shed into the circulation by proteolytic processing of the sheddase a disintegrin and metalloproteinase 10 (ADAM 10).¹¹ Although they may reflect the activity of the AGE–RAGE axis and act as decoys that neutralize the actions of AGEs in the circulation,^{12–14} the functional role of these soluble forms of RAGE in plaque vulnerability remains unclear in patients with AMI.

In this study, we measured the plasma levels of MMP-9, sRAGE, and esRAGE in AMI patients to evaluate the biological effects of these molecules on plaque vulnerability.

Methods

Patient Selection

Of 1,282 patients who underwent coronary angiography (CAG) between October 2007 and December 2008 at Seoul St Mary's Hospital, we enrolled 54 patients with AMI (27 patients had type 2 DM) who underwent primary percutaneous coronary intervention (PCI) within 12h of the onset of

chest pain. As a control group, we selected 54 patients with normal CAG who were matched for age, gender, and the presence of DM.

AMI was diagnosed based on chest pain persisting for 30 min and elevation of the serum creatine kinase (CK-MB) level to more than twice the upper limit of normal. Patients with ST elevation MI (STEMI) and non-STEMI (NSTEMI) were included in this study. DM was diagnosed by demonstrating any one of the following: (1) symptoms of hyperglycemia and a random plasma glucose ≥ 200 mg/dl; (2) fasting plasma glucose level ≥ 126 mg/dl; and (3) plasma glucose ≥ 200 mg/dl at 2 h after a 75-g oral glucose load in a glucose tolerance test.¹⁵

We excluded patients who had comorbidities, such as acute and/or chronic infections, inflammatory diseases, malignancies, ongoing liver disease and/or abnormal liver function tests (serum aspartate aminotransferase or alanine aminotransferase > 3 -fold the upper limit of normal), and renal insufficiency (serum creatinine > 2.5 mg/dl).

Data Collection and Factor Measurements

Clinical, laboratory, and medication histories were obtained through a comprehensive review of each patient's medical records, including case notes from the hospital's computerized patient information system. Hypertension was defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg and/or use of antihypertensive drugs. Hyperlipidemia was defined as total cholesterol level ≥ 240 mg/dl or triglyceride level ≥ 200 mg/dl, and/or the use of any relevant drugs. Current smoking referred to the active use of tobacco products at the time of enrollment in the study. Hemoglobin, serum creatinine, fasting lipid profiles, and levels of glycosylated hemoglobin (HbA_{1c}) and C-reactive protein (CRP) were obtained at the time of CAG. Plasma levels of MMP-9, sRAGE (R&D Systems, Minneapolis, MN, USA) and esRAGE (B-Bridge International, Sunnyvale, CA, USA) were measured by enzyme-linked immunosorbent assays using the blood samples obtained from each patient through the introducer sheath placed in the femoral artery at the time of CAG. Informed consent was given by each patient and the study protocol was approved by the institutional review board of Seoul St Mary's Hospital, Catholic University of Korea.

Statistical Analysis

Analysis of categorical data to identify statistically significant differences between groups was performed using the chi-square test. Continuous variables are presented as the mean $\pm$ standard deviation and were compared by Student's t-test or 1-way ANOVA. To identify independent predictors of AMI, both uni- and multivariate logistic regression analyses were performed for these subjects. Covariates statistically significant on univariate analysis ($P < 0.1$) were considered as candidate variables in the multivariate models. Statistical analyses were performed with SPSS (version 15.0; SPSS Inc, Chicago, IL, USA). For all analyses, $P < 0.05$ was considered statistically significant.

Results

Table 1 shows the baseline characteristics of the AMI group and controls at the time of CAG. There were no significant differences between the groups, with the exception of the serum CRP level (14.1 ± 14.2 vs. 3.7 ± 5.2 mg/L, $P < 0.001$). The body mass index was lower and the proportion of current smokers was higher in the AMI group than in the controls,

Figure 1. Comparison of the plasma levels of MMP-9 and s/esRAGE in the AMI group and controls. AMI, acute myocardial infarction; MMP, matrix metalloproteinases; s/esRAGE, soluble/endogenous secretory receptors for advanced glycation endproducts.

although statistically insignificant.

The plasma levels of MMP-9 (28.6 ± 21.4 vs. 14.3 ± 8.5 ng/ml, $P < 0.001$) and sRAGE (0.61 ± 0.28 vs. 0.41 ± 0.17 ng/ml, $P < 0.001$) were higher in the AMI group than in the controls. However, the plasma level of esRAGE was similar between the groups (0.29 ± 0.23 vs. 0.31 ± 0.25 ng/ml, $P = 0.793$; **Figure 1**). In subgroup analysis according to the presence of DM, the plasma levels of MMP-9 and sRAGE were also higher in the AMI group than in the controls, regardless of the presence of DM (**Figure 2**).

Table 2 gives the odds ratios (ORs) of AMI in patients with prespecified risk factors at the time of the CAG. Based on univariate logistic regression analysis, a plasma level of $\text{CRP} \geq 3.0$ mg/L, and MMP-9 and sRAGE levels above the median were significant independent predictors of AMI ($P < 0.05$). Current smokers were also identified in a broader range of variables ($P < 0.1$) that might be associated with AMI. Based on multiple logistic regression analysis, plasma levels of MMP-9 and sRAGE above the median (OR, 2.39; 95%

confidence interval [CI], 1.02–5.58; $P = 0.044$; and OR, 2.47; 95% CI, 1.05–5.80; $P = 0.039$, respectively) were significantly associated with AMI, as well as being a current smoker (OR, 2.98; 95% CI, 1.18–7.55; $P = 0.021$) and having a $\text{CRP} \geq 3.0$ mg/L (OR, 3.08; 95% CI, 1.25–7.59; $P = 0.015$).

Discussion

In the present study, we report that plasma levels of MMP-9 and sRAGE were significantly higher in the AMI group than in the controls, independent of the presence of DM. However, plasma levels of esRAGE showed no differences between the groups. Moreover, plasma levels of MMP-9 and sRAGE above the median were significant predictors of AMI, as well as being a current smoker and having a $\text{CRP} \geq 3.0$ mg/L. These findings suggest that the plasma level of sRAGE is positively associated with AMI and that RAGE-dependent inflammatory responses might contribute to plaque vulnerability, along with MMP-9. This is the first report to evaluate

the biological roles of sRAGE in AMI patients who have undergone primary PCI.

An AMI is thought to be the result of an under-exaggerated inflammatory state that destabilizes the fibrous cap tissue and thus enhances the risk of coronary thrombosis.³ MMPs are significant cytokines, mainly produced by infiltrating inflammatory cells and can degrade the strength-giving collagens and other structural proteins of the arterial extracellular matrix. Overproduction of MMPs by monocytes/macrophages could therefore promote rupture of atherosclerotic plaque rupture and subsequent MI.¹⁶ Among the various MMPs, MMP-9 may play an important role in plaque rupture because of its broad substrate specificity and its position in the matrix proteolytic cascade.¹⁷ Some clinical studies have reported that MMP-9 is significantly elevated in patients with acute coronary syndrome, including AMI.^{18,19} A recent virtual histology intravascular ultrasound study also showed that the plasma MMP-9 level was increased in patients with multiple ruptured plaques, as well as in patients with a ruptured plaque among the culprit lesions.²⁰ Consistent with previous reports, our data also showed that the plasma level of MMP-9 was

significantly higher in the AMI group than in the controls.

The CRP level, which is a marker of underlying systemic inflammation, is also an independent clinical predictor of plaque rupture in AMI patients. In a pathologic study, using immunohistochemical staining for CRP, of patients who died suddenly associated with severe CAD has reported that CRP may correlate with the number of thin-capped fibroatheromas, which can be considered as vulnerable plaque.²¹ Several IVUS studies also have showed that ruptured plaque and/or vulnerable plaque exist not only at the culprit lesion but also in a pan-coronary artery setting in patients with AMI and elevated CRP level.^{22–24} Recently, Kashiwagi et al reported that positive arterial remodeling in IVUS, a thin fibrous cap thickness in optical coherence tomography, and a high CRP level were associated with each other in patients with acute coronary syndrome.²⁵ Their findings are consistent with our results that the serum CRP level was significantly higher in the AMI group than in the controls, and an elevated CRP level (≥ 3 mg/L) was an independent predictor of AMI.

Recent clinical studies have investigated the potential significance of circulating sRAGE and esRAGE concentrations

Table 2. OR for AMI in Patients With Each Prespecified Risk Factor at the Time of Coronary Angiography (Uni- and Multi-Variate Logistic Regression Analyses)

	Univariate			Multivariate		
	OR	95%CI	P value	OR	95%CI	P value
Clinical variables						
Age ≥ 65 years	1.16	0.55–2.47	0.700			
BMI ≥ 25 kg/m ²	0.59	0.27–1.27	0.173			
Hypertension	0.93	0.44–1.98	0.847			
Hyperlipidemia	1.72	0.61–4.83	0.305			
Current smoker	2.08	0.93–4.64	0.073	2.98	1.18–7.55	0.021
Laboratory variables						
Hemoglobin < 12 g/dl	1.92	0.69–5.32	0.211			
eGFR < 60 ml $\cdot$ min ⁻¹ $\cdot$ 1.73 m ²	1.15	0.41–3.25	0.792			
TC ≥ 240 mg/dl	1.59	0.34–7.50	0.560			
TG ≥ 200 mg/dl	0.89	0.38–2.08	0.782			
HDL < 40 mg/dl	0.93	0.40–2.12	0.856			
LDL ≥ 130 mg/dl	1.53	0.55–4.27	0.419			
CRP ≥ 3.0 mg/L	3.14	1.43–6.91	0.004	3.08	1.25–7.59	0.015
HbA _{1c} $\geq 7.0\%$	0.55	0.18–1.66	0.286			
MMP-9 $\geq$ median cut-off	2.47	1.14–5.35	0.022	2.39	1.02–5.58	0.044
sRAGE $\geq$ median cut-off	3.13	1.43–6.87	0.004	2.47	1.05–5.80	0.039

OR, odd ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate by Modification of Diet in Renal Disease (MDRD) formula; MMP-9, matrix metalloproteinase-9; sRAGE, soluble receptor of advanced glycosylated endproducts. Other abbreviations see in Table 1.

in several pathologic conditions, particularly atherosclerotic vascular disease.^{26–29} In CAD, some clinical studies have shown that a lower level of plasma sRAGE is inversely associated with the severity of CAD.^{28,29} However, other reports have shown that serum sRAGE levels are significantly higher in patients with type 2 DM than in non-diabetic subjects, and positively associated with the presence of CAD.³⁰ The same authors also demonstrated that the sRAGE level positively correlated with circulating levels of AGEs and soluble forms of vascular cell adhesion molecule-1, suggesting that the sRAGE level may be elevated in response to circulating AGEs, thereby constituting a novel marker of vascular injury in patients with DM.³¹ In the present study, we demonstrated that the plasma level of sRAGE was positively associated with AMI, but not that of esRAGE. These findings suggested that in patients with an AMI, an enhanced AGE–RAGE interaction may increase the inflammatory response in vulnerable plaques, together with plasma levels of sRAGE, but it does not efficiently capture or eliminate circulating AGEs in vivo by acting as a decoy receptor.³² In addition, sRAGE and esRAGE may exert different biological effects on plaque vulnerability in patients with AMI, even though they may act in a very similar way as decoys that neutralize the actions of AGEs. In fact, the endogenous action of sRAGE may not be confined to a decoy function against RAGE signaling. Pullerits et al reported that sRAGE interacts with Mac-1 and is mediated via nuclear factor- κ B to act as important pro-inflammatory and chemotactic molecules in an HMGB1-induced arthritis model.³³

Interestingly, in a subgroup analysis of our study patients with AMI, there were no significant correlations between the plasma levels of MMP-9 and sRAGE ($r = -0.080$, $P = 0.563$) or those of CRP and sRAGE ($r = 0.022$, $P = 0.877$). This finding was inconsistent with a recent study that showed sRAGE was negatively correlated with MMP-9 ($r = -0.419$, $P < 0.01$) and CRP ($r = -0.326$, $P < 0.01$) in non-diabetic patients with premature CAD.²⁹ The difference in the results might be

caused by the different clinical settings of AMI and premature CAD. Unlike MMP-9 and CRP, sRAGE may have dual functions as a decoy and/or trigger of inflammation, and the net effect of sRAGE and its ligand interactions can be anti- or pro-inflammatory depending on the inflammatory milieu.³³ In the disease subset of AMI, the role of sRAGE may outweigh its pro-inflammatory properties, even though the decoy function of sRAGE may attenuate the positive correlation with MMP-9 and CRP to some degree. However, further studies are needed to provide more clarity about the biological mechanisms underlying the kinetics of sRAGE production and removal in both health and disease states.

In conclusion, the plasma level of sRAGE was significantly higher in the AMI group than in the controls, and this elevated sRAGE concentration may be independently associated with plaque vulnerability in patients with AMI.

Study Limitations

First, this study was a case-control design and examined a relatively small number of subjects, despite the selection of the control group after matching for age, gender, and the presence of DM. Therefore, it was difficult to identify a cause and effect relationship between MMP-9 and sRAGE on plaque vulnerability in the current study. Second, we were unable to measure plasma concentrations of AGEs and/or tissue RAGE expression, which could provide a better understanding of the relationship between the activities of the AGE–RAGE axis, the soluble forms of RAGE, and AMI. Finally, plaque rupture is a local event that develops in highly inflamed vulnerable plaque in human coronary arteries. Therefore, associated molecules may be increased or attenuated in the local milieu, but we used blood samples obtained from each patient when the introducer sheath was placed in the femoral artery at the time of the index procedure. Samples taken from this location may not necessarily demonstrate a gradient because of dilution and washout effects.

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