Soluble Receptors for Advanced Glycation End Products (sRAGE) as a Predictor of Restenosis Following Percutaneous Coronary Intervention

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ABSTRACT

Background: Interaction of advanced glycation end products (AGEs) with their receptor (RAGE) increases expression of inflammatory mediators (tumor necrosis factor alpha [TNF- α] and soluble vascular cell adhesion molecule-1 [sVCAM-1]) and induces oxygen radicals that are implicated in atherosclerosis. Balloon-injury-induced atherosclerosis is associated with increased expression of AGEs and RAGE. The soluble receptor for AGE (sRAGE), which acts as a decoy for RAGE ligands (AGEs), prevents atherosclerosis in this model.

Hypothesis: We evaluated: 1) whether post-percutaneous coronary intervention (PCI) restenosis is associated with low pre-PCI serum sRAGE, high serum AGEs, TNF- α , and sVCAM-1, and high AGE/sRAGE ratio; 2) whether pre-PCI and post-PCI levels of these markers are similar in patients with or without restenosis; and 3) whether sRAGE and AGE/sRAGE ratio have predictive value for post-PCI restenosis.

Methods: Angiography was performed in 46 patients with non-ST-segment elevation myocardial infarction for assessment of restenosis. Serum sRAGE, AGEs, TNF- α , and sVCAM-1 were measured in these patients and 20 control subjects.

Results: Nineteen of the 46 patients developed post-PCI restenosis, which was associated with lower sRAGE and higher TNF- α and sVCAM-1 levels, and higher AGE/sRAGE ratio compared with patients without restenosis. Pre-PCI and post-PCI levels of these biomarkers were similar in both groups, except in patients with restenosis, in whom the post-PCI level of sRAGE was lower and TNF- α was higher than the pre-PCI levels. The sensitivity and negative predictive value of sRAGE were 100%, and were higher than those of AGE/sRAGE ratio in identifying post-PCI restenosis.

Conclusions: Both low serum sRAGE levels and high AGE/sRAGE ratio have predictive value for post-PCI restenosis.

Introduction

Advanced glycation end products (AGEs) are formed from the nonenzymatic glycation and oxidation of proteins, lipids, and nucleic acids.^{1,2} AGEs interact with 3 types of cell receptors for advanced glycation end products (RAGE), namely full-length RAGE and N-truncated and C-truncated soluble receptors for AGEs (sRAGE).^{2–5} The interaction of full-length RAGE with AGEs increases the expression of adhesion molecules, including soluble vascular cell adhesion molecule-1 (sVCAM-1) and the cytokine tumor necrosis factor alpha (TNF- α),^{2,6,7} the activation of nuclear factor kappa B (NF- κ B),⁷ which in turn increases the expression of proinflammatory genes for

adhesion molecules and cytokines^{2,8} and the generation of reactive oxygen species.⁹ The function of membrane-bound N-truncated RAGE is poorly understood. Circulating in the plasma, sRAGE is not membrane-bound⁴ and it acts as a decoy for RAGE ligands (AGE) and competes with full-length RAGE for ligand binding.¹⁰

Adhesion molecules, cytokines, and reactive oxygen species are involved in the development and progression of atherosclerosis and lesion instability.^{11,12} AGEs and RAGE axis is involved in the development of atherosclerosis in diabetes.^{13,14} Balloon injury in carotid artery and endothelial denudation in animal models increase the levels of RAGE and AGEs in the arterial wall and produce neointimal hyperplasia.^{15,16} Treatment with sRAGE in animal models reduces neointimal growth, decreases proliferation and migration of smooth muscle cells, and decreases expression of extracellular matrix.^{15,16} Also, sRAGE reduces the atherosclerotic lesions in apolipoprotein E (apo E)^{–/–} mice, and this effect is associated with a decrease in aortic VCAM-1 and tissue factor.^{16–18}

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Restenosis is a major adverse outcome for long-term success after percutaneous coronary interventions (PCI) such as angioplasty and stenting.¹⁹ The incidence of restenosis is between 35% and 45% with bare-metal stents and <10% with drug-eluting stents.^{20,21} Post-PCI restenosis is associated with neointimal hyperplasia.^{22,23}

It is hypothesized that post-PCI restenosis may be due to low levels of serum sRAGE and increased interaction between RAGE and AGE leading to enhanced expression of inflammatory mediators, culminating in the development of restenosis. The main objectives of the present study were to determine: 1) whether pre-PCI serum levels of sRAGE are lower and levels of sVCAM-1, TNF- α , AGE, and the AGE/sRAGE ratio are higher in non-ST-segment elevation myocardial infarction (NSTEMI) subjects who develop post-PCI restenosis compared with those who do not; 2) the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of the sRAGE and AGE/sRAGE ratio tests in predicting post-PCI restenosis; and 3) whether the pre-PCI levels of sRAGE or the AGE/sRAGE ratio are better predictors for post-PCI restenosis.

Methods

Patient Population

The study population consisted of 46 consecutive NSTEMI patients admitted to the Royal University Hospital, Saskatoon, Saskatchewan. The demographic and clinical characteristics of the patients with and without restenosis are summarized in the Table 1. All patients in the study met the following inclusion criteria: 1) acute coronary syndrome patients of the NSTEMI subclass; 2) discrete de novo localized lesions in a single vessel, 2 vessels, or 3 vessels; 3) patients who received implantation of bare-metal stents; 4) aged 40–70 years; 5) nondiabetic; and 6) male gender. The exclusion criteria for patients in the study were as follows: 1) artery reference diameter <2.5 mm, 2) acute myocardial infarction (MI) within the previous 5 days, 3) post-coronary artery bypass graft surgery, 4) diabetic, 5) female gender, 6) coexisting cardiomyopathy, 7) coexisting inflammatory diseases, 8) coexisting valvular disease, 9) a history of substance abuse, and 10) patients living >3 hours outside the Saskatoon metropolitan area (who were less likely to return for follow-up). The control group consisted of 28 age-matched healthy males who had no history of the following: 1) heart disease, 2) hypertension, 3) diabetes, 4) inflammatory diseases, or 5) current smoking habits, and who 6) had a normal electrocardiogram. The study protocol was approved by the Ethics Committee for Human Studies at the University of Saskatchewan and Royal University Hospital, Saskatoon. Written informed consent was obtained from each patient. Investigators were in accordance with the Declaration of Helsinki.

Table 1. Demographic and Clinical Characteristics of Control Subjects, Patients With Restenosis, and Patients Without Restenosis

Parameter	Control n = 28	With Restenosis n = 19	Without Restenosis n = 27
TC (mmol/L)	4.4 $\pm$ 0.25	6.0 $\pm$ 0.30 ^a	4.5 $\pm$ 0.20 ^b
HDL-C (mmol/L)	1.35 $\pm$ 0.14	0.9 $\pm$ 0.10 ^a	1.0 $\pm$ 0.10
LDL-C (mmol/L)	2.78 $\pm$ 0.10	4.38 $\pm$ 0.40 ^a	3.8 $\pm$ 0.33 ^a
TG (mmol/L)	2.19 $\pm$ 0.30	2.5 $\pm$ 0.30	2.4 $\pm$ 0.4
CTnI (μ g/L)	NA	2.74 $\pm$ 0.34	2.83 $\pm$ 0.52
Cholesterol risk ratio	3.89 $\pm$ 0.33	3.92 $\pm$ 0.37	4.65 $\pm$ 0.52
Fasting glucose (mmol/L)	4.8 $\pm$ 0.32	5.4 $\pm$ 0.22	5.5 $\pm$ 0.25
Hs CRP (mg/L)	3.05 $\pm$ 0.26	12.3 $\pm$ 3.4 ^a	8.4 $\pm$ 3.6 ^{a,b}
BMI (kg/m ²)	25 $\pm$ 1.5	25 $\pm$ 1.5	29 $\pm$ 0.70
BP (mm Hg)			
Systolic	125 $\pm$ 22	148 $\pm$ 19.7 ^a	153 $\pm$ 24 ^a
Diastolic	78 $\pm$ 5.5	74 $\pm$ 3.4	70 $\pm$ 5.2
Mean	90 $\pm$ 3.3	90 $\pm$ 4.2	91 $\pm$ 3.8
Age (y)	60 $\pm$ 2.0	61.5 $\pm$ 2.9	66.1 $\pm$ 1.9

Abbreviations: BMI, body mass index; BP, blood pressure; CTnI, cardiac troponin I; HDL-C, high-density lipoprotein cholesterol; Hs CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; NA, not applicable; TC, total cholesterol; TG, triglycerides. Results are expressed as mean $\pm$ SEM.

^a $P < 0.05$, control vs other groups.

^b $P < 0.05$, with restenosis vs without restenosis.

Coronary Angiography

Coronary angiography was performed and the angiograms were interpreted by 2 cardiologists blinded to the clinical characteristics of the patients. Reference diameters, minimal lumen diameter, percentage of stenosis, and lesion length were measured using a semiautomated edge counter detection computer analysis system (DCI-ACA quantitative coronary angiography system; Philips, Eindhoven, The Netherlands). A significant obstructive atherosclerotic lesion was defined as stenosis $\geq 50\%$ of the luminal diameter in 1 or more coronary arteries. Angina with angiographic evidence of >50% narrowing of the vessel was taken as a criterion for post-PCI restenosis.²⁴

Percutaneous Coronary Intervention

All procedures for stent implantation were performed according to standard techniques. Bare-metal stents were

implanted in all 46 NSTEMI patients. Angiographic success was defined as residual stenosis of <20%. Recommended postprocedural medications included lifelong low-dose acetylsalicylic acid (81 mg/d) and clopidogrel (75 mg/d) for 1 year. A loading dose of 300 mg clopidogrel was administered pre-PCI in some patients who had never taken clopidogrel before. Follow-up medications included lipid-lowering and antihypertensive agents.

Biochemical Measurements

Blood samples were collected for the measurement of serum AGE, sRAGE, TNF- α , sVCAM-1, lipids, cardiac troponin I (CTnI), and glucose. Serum sRAGE, TNF- α , and sVCAM-1 were measured using commercially available enzyme-linked immunoassay (ELISA) kits (R&D Systems, Minneapolis, MN). Serum AGE levels were measured using a commercially available ELISA kit (BioPCR; Beijing Zhonghao Shidai Co., Ltd., Beijing, China). Serum total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), and glucose were measured on a Beckman DX 800 (Beckman Coulter, Inc., Fullerton, CA) using standard laboratory protocol. CTnI was measured using an Abbott Architect (i2000SR; Abbott Laboratories, Chicago, IL).

Sensitivity, specificity, PPV, NPV, and accuracy of the pre-PCI sRAGE and AGE/sRAGE ratio tests in predicting post-PCI restenosis were calculated using the methods described by Glas et al.²⁵ The mean (–) 1.645 SD (702 pg/mL) for sRAGE and mean (+) 1.645 SD (2.28) for AGE/sRAGE ratio, which cover 90% of the patients without restenosis, were taken as the cutoff points.

Statistical Analysis

Sample size was calculated using a 2-sided Satterthwaite *t* test to have 95% power and a 5% alpha level. Results are presented as mean $\pm$ SE. The data between the 2 groups were compared using a 2-tailed unpaired Student *t* test. Single linear univariate correlations (Pearson's correlation coefficients) were performed to evaluate the relationship between serum sRAGE and the following variables: serum TNF- α , sVCAM-1, AGE, and the AGE/sRAGE ratio.

Results

The baseline characteristics of the patients without or with restenosis and control subjects are summarized in the Table. There were no significant differences in age, blood pressure, body mass index, serum glucose, HDL-C, LDL-C, TG, TC, risk ratio, and CTn-I between the 2 patient groups. However, serum levels of high-sensitivity C-reactive protein (hs-CRP) and TC were lower in patients without restenosis. The levels of serum LDL-C, hs-CRP, CTn-I, and blood pressure were higher in both groups compared with the control group.

Pre-PCI Levels of Serum sRAGE, TNF- α , sVCAM-1, and AGE, and the AGE/sRAGE Ratio in Patients With or Without Restenosis and Control Subjects

The levels of serum sRAGE, AGE, TNF- α , and sVCAM-1, and the AGE/sRAGE ratio in patients with and without restenosis and in control subjects are summarized in Figure 1. The pre-PCI serum sRAGE levels in control subjects, patients without stenosis, and patients with restenosis were 1287 ± 41.5 pg/mL, 1143.8 ± 52.5 pg/mL, and 610.6 ± 24.1 pg/mL, respectively. The values were significantly ($P < 0.001$) lower in patients with restenosis compared with the values in patients without restenosis and the control subjects.

The pre-PCI levels of serum AGE in patients without restenosis were not significantly different from those in control subjects (981.7 ± 92.4 ng/mL vs 669.40 ± 47.9 ng/mL). However, the levels of AGE were significantly higher in patients with restenosis compared with control subjects (1512.1 ± 84.3 ng/mL vs 669.4 ± 47.9 ng/mL) and compared with patients without restenosis (1512.1 ± 84.53 ng/mL vs 891.7 ± 92.4 ng/mL).

The pre-PCI AGE/sRAGE ratio was significantly higher in patients with or without restenosis (2.39 ± 0.20 and 1.03 ± 0.17 , respectively) compared with control subjects (0.54 ± 0.06). Also, the AGE/sRAGE ratio was higher in patients with restenosis than in those without restenosis.

The levels of TNF- α were higher in patients with restenosis as compared with patients without restenosis (37.9 ± 2.5 pg/mL vs 11.6 ± 0.41 pg/mL) and control subjects. The levels were not significantly different between the patients without restenosis and the control subjects. The serum levels of sVCAM-1 in patients with restenosis were higher than those in patients without restenosis (1381.8 ± 63.5 ng/mL vs 811.37 ± 26.5 ng/mL).

Pre-PCI and Post-PCI Serum sRAGE, TNF- α , and sVCAM-1 in Patients With or Without Restenosis

These studies were conducted to determine whether the pre-PCI serum levels of sRAGE, TNF- α , and sVCAM-1 are different from the post-PCI levels in patients with or without restenosis. The results are summarized in Figure 2. The post-PCI levels of sRAGE were lower and the post-PCI levels of TNF- α higher in patients with restenosis. The pre-PCI and post-PCI levels of sVCAM-1 were similar in patients with restenosis. The pre-PCI and post-PCI levels of sRAGE, TNF- α , and sVCAM-1 were similar in patients without restenosis.

Correlation of Pre-PCI sRAGE vs TNF- α and sVCAM-1, and of Post-PCI sRAGE vs TNF- α and sVCAM-1 in Patients With Restenosis

The results are summarized in Figure 3. The levels of serum sRAGE are negatively correlated with the levels of TNF- α and sVCAM-1, irrespective of pre-PCI or post-PCI measurement.

Figure 1. Pre-PCI serum levels of sRAGE, AGE, TNF- α , and sVCAM-1, and the pre-PCI AGE/sRAGE ratio in control subjects and patients without (–) and with (+) post-PCI restenosis. Results are expressed as mean $\pm$ SE.

Abbreviations: AGE, advanced glycation end products; PCI, percutaneous coronary intervention; sRAGE, soluble receptor for advanced glycation end products; sVCAM-1, soluble vascular cell adhesion molecule-1; TNF- α , tumor necrosis factor alpha.

^a $P < 0.05$, control vs with or without restenosis.

^b $P < 0.05$, with vs without restenosis.

Correlation of Pre-PCI or Post-PCI sRAGE With Pre-PCI or Post-PCI TNF- α and sVCAM-1 in Patients Without Restenosis

The results are summarized in Figure 4. The serum levels of sRAGE are negatively correlated with the levels of TNF- α and sVCAM-1, irrespective of pre-PCI or post-PCI measurements.

Sensitivity, Specificity, PPV, NPV, and Accuracy of the Pre-PCI sRAGE and AGE/sRAGE Ratio Tests

The sensitivity, specificity, PPV, NPV, and accuracy of the pre-PCI sRAGE test were 100%, 83%, 85%, 100%, and 91%, respectively, in identifying patients who developed post-PCI restenosis. The sensitivity, specificity, PPV, NPV, and accuracy of the AGE/sRAGE ratio test were 81%, 94%, 93%, 84%, and 88%, respectively, in identifying patients who developed post-PCI restenosis.

Discussion

Post-PCI Restenosis

In the present study, the restenosis rate was 41%. Rates of in-stent restenosis with bare-metal stents have been reported to range from 30% to 45%.^{20,21,26} Other studies have reported restenosis rates as high as 51%.²⁷

sRAGE and AGE

We have shown for the first time that pre-PCI and post-PCI levels of serum sRAGE are lower whereas levels of AGE and the AGE/sRAGE ratio are higher in NSTEMI patients with post-PCI restenosis compared with patients without restenosis. Post-PCI levels of sRAGE were lower in patients with restenosis compared with patients without restenosis. Lower levels of serum sRAGE in patients with coronary artery disease compared with control subjects have been

Figure 2. Pre-PCI and post-PCI levels of sRAGE, TNF- α , and sVCAM-1 in patients with and without restenosis. Results are expressed as mean $\pm$ SE. Abbreviations: PCI, percutaneous coronary intervention; sRAGE, soluble receptor for advanced glycation end products; sVCAM-1, soluble vascular cell adhesion molecule-1; TNF- α , tumor necrosis factor alpha. ^a $P < 0.05$, pre-PCI vs post-PCI.

reported²⁸, however, these were not NSTEMI patients. The mechanism for low serum sRAGE in patients who developed restenosis or NSTEMI patients compared with control subjects cannot be explained at present. Increases in the serum levels of AGE and the AGE/sRAGE ratio may be due to atherosclerotic lesions. It is known that endothelial injury increases the levels of AGEs in the arterial wall.^{15,16}

TNF- α

We are the first to show that pre-PCI and post-PCI levels of serum TNF- α are higher in NSTEMI patients with restenosis than in NSTEMI patients without restenosis. There are, however, reports of elevated levels of serum TNF- α in ST-segment elevation myocardial infarction (STEMI) patients.²⁹ The serum levels of sRAGE were negatively correlated with serum levels of TNF- α .

sVCAM-1

We also show that the pre-PCI levels of serum sVCAM-1 are higher in patients with restenosis compared with patients without restenosis. Elevated levels of serum sVCAM-1 have been reported in STEMI patients.³⁰ There was an inverse relationship between sRAGE and sVCAM-1 in the present

study. Nuclear extracts from AGE-treated endothelial cells result in increased expression of endothelial cell sVCAM-1.³¹ They also reported that sRAGE blocks the expression of sVCAM-1. Pre-PCI and post-PCI levels of sVCAM-1 were similar in patients with or without restenosis.

sRAGE and AGE Axis and Atherosclerosis

The data suggest that low levels of sRAGE are associated with high levels of serum TNF- α , sVCAM-1, AGE, and AGE/sRAGE in NSTEMI patients with post-PCI restenosis. An increase in AGE will increase the interaction between AGE and RAGE, which will culminate in increased production of TNF- α and sVCAM-1. TNF- α may induce restenosis in several ways. TNF- α stimulates superoxide anion (O_2^-) production in neutrophils and endothelial cells via nicotinamide adenine dinucleotide phosphate oxidase,³² xanthine oxidase,³³ and nitric oxide (NO) synthase.³⁴ TNF- α activates NF- κ B, which regulates the expression of genes involved in inflammation and oxidative stress.³⁵ TNF- α decreases the bioavailability of NO by decreasing the production of NO³⁶ and enhancing the removal of NO.³⁷ Oxidative stress^{12,38} and deficiency of NO³⁹ have been implicated in the development of atherosclerosis.

Figure 3. Correlation of pre-PCI or post-PCI sRAGE with pre-PCI or post-PCI TNF- α ; and sVCAM-1 in patients with restenosis. Abbreviations: PCI, percutaneous coronary intervention; sRAGE, soluble receptor for advanced glycation end products; sVCAM-1, soluble vascular cell adhesion molecule-1; TNF- α , tumor necrosis factor alpha.

Adhesion molecules, including sVCAM-1, are involved in the development of atherosclerosis.¹¹ Involvement of sRAGE in restenosis is also supported by the fact that sRAGE in the animal model reduces the development of balloon-injury-induced atherosclerosis and atherosclerotic lesion in apo E $^{-/-}$ mice, and this effect was associated with a decrease in sVCAM-1.^{15–17}

Sensitivity, Specificity, Predictive Values, and Accuracy of the sRAGE and AGE/sRAGE Ratio Tests

Both sRAGE and AGE/sRAGE ratio tests have good sensitivity, specificity, predictive values, and accuracy in identifying the patients who may develop post-PCI restenosis. There is no other test available to predict post-PCI restenosis.

Conclusion

In conclusion, the serum levels of sRAGE are lower, and the levels of AGE, TNF- α , and sVCAM-1 and the AGE/sRAGE ratio are higher in NSTEMI patients with post-PCI restenosis compared with patients without restenosis. The sensitivity, specificity, predictive values, and accuracy of the sRAGE and AGE/sRAGE ratio tests are

valuable in identifying patients who may develop post-PCI restenosis.

Clinical Application (From Bench to Bedside)

Based on the sample size of the present study, the cutoff point for sRAGE below in which the patient has a 95% chance of developing post-PCI restenosis is mean + 2 SD (610.6 + 204.49) pg/mL, or 814.5 pg/mL. The cutoff point for the AGE/sRAGE ratio above in which the patient has a 95% chance of developing post-PCI restenosis is mean – 2 SD (2.39–1.68), or 0.71. There is no other test available to predict post-PCI restenosis. These tests will be useful in predicting post-PCI restenosis and may help in directing and developing treatment modalities for reducing serum AGE and increasing serum sRAGE, hence preventing post-PCI restenosis.

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Figure 4. Correlation of pre-PCI or post-PCI sRAGE with pre-PCI or post-PCI TNF- α ; and sVCAM-1 in patients without restenosis. Abbreviations: PCI, percutaneous coronary intervention; sRAGE, soluble receptor for advanced glycation end products; sVCAM-1, soluble vascular cell adhesion molecule-1; TNF- α , tumor necrosis factor alpha.

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