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Effect of statins on the serum soluble form of receptor for advanced glycation end-products and its association with coronary atherosclerosis in patients with angina pectoris

Tsuyoshi Nozue [a,*,1], Sho-ichi Yamagishi [b,1], Masayoshi Takeuchi [c,1], Tsutomu Hirano [d,1], Shingo Yamamoto [e,1], Shinichi Tohyama [f,1], Kazuki Fukui [g,1], Shigeo Umezawa [h,1], Yuko Onishi [h,1], Tomoyuki Kunishima [i,1], Kiyoshi Hibi [j,1], Mitsuyasu Terashima [k,1], Ichiro Michishita [a,1]

[a] Division of Cardiology, Department of Internal Medicine, Yokohama Sakae Kyosai Hospital, Yokohama, Japan
[b] Department of Pathophysiology and Therapeutic of Diabetic Vascular Complications, Kurume University School of Medicine, Kurume, Japan
[c] Department of Advanced Medicine, Medical Research Institute, Kanazawa Medical University, Uchinada, Japan
[d] First Department of Internal Medicine, Showa University School of Medicine, Tokyo, Japan
[e] Department of Cardiology, Tsurumi Nishiguchi Hospital, Yokohama, Japan
[f] Department of Cardiology, Yokohama Seamen's Insurance Hospital, Yokohama, Japan
[g] Department of Cardiology, Kanagawa Cardiovascular and Respiratory Center, Yokohama, Japan
[h] Department of Cardiology, Hiratsuka Kyosai Hospital, Hiratsuka, Japan
[i] Fourth Department of Internal Medicine, Mizonokuchi Hospital, Teikyo University School of Medicine, Kawasaki, Japan
[j] Division of Cardiology, Yokohama City University Medical Center, Yokohama, Japan
[k] Cardiovascular Imaging Center, Toyohashi, Japan

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ABSTRACT

Background: Advanced glycation end-products (AGEs) and their receptor (RAGE) play an important role in the pathogenesis of diabetic vascular complications. Recently, soluble form of RAGE (sRAGE) has been identified in mice and humans. Statins have been reported to increase serum sRAGE levels. However, whether modulation of circulating sRAGE levels has a beneficial effect on the progression of atherosclerosis is unknown.
Methods: We reviewed 91 patients who had undergone percutaneous coronary intervention for angina pectoris. Coronary atherosclerosis in non-culprit lesions in the target vessel was evaluated, using virtual histology intravascular ultrasound, and serum levels of AGEs and sRAGE were measured, at baseline and after 8 months of statin therapy.
Results: Statins had no effects on serum AGEs levels; however, serum levels of sRAGE were significantly higher at the 8-month follow-up. A significant decrease in external elastic membrane (EEM) volume (−1.6%, $p = 0.005$) was observed, whereas a decrease in plaque volume did not reach statistical significance (−1.9%, $p = 0.16$). Univariate regression analyses showed that the percentage changes in serum sRAGE were negatively correlated with those in EEM volume ($r = -0.198$, $p = 0.06$) and plaque volume ($r = -0.247$, $p = 0.02$). Multivariate regression analysis showed that an increase in serum sRAGE level was an independent predictor of atheroma regression after statin therapy ($\beta = -0.290$, $p = 0.006$).
Conclusions: Statin therapy increased serum sRAGE levels, and this increase was associated with negative vessel remodeling and atheroma regression in the coronary artery.

1. Introduction

Advanced glycation end-products (AGEs) and their receptor (RAGE) play an important role in the pathogenesis of diabetic vascular complications [1–3]. Recently, soluble form of RAGE (sRAGE) has been identified in mice and humans [4]. Administration of a recombinant sRAGE has been shown to suppress the development of atherosclerosis as

* Corresponding author at: Division of Cardiology, Department of Internal Medicine, Yokohama Sakae Kyosai Hospital, Federation of National Public Service Personnel Mutual Associations, 132 Katsura-cho, Sakae-ku, Yokohama 247-8581, Japan. Tel.: +81 45 891 2171; fax: +81 45 895 8352.
E-mail address: nozue2493@yahoo.co.jp (T. Nozue).
[1] All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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well as to stabilize established atherosclerosis in diabetic apolipoprotein (apo) E-null mice [5,6]. These observations suggest that sRAGE acts as a decoy receptor for AGEs. However, since AGEs up-regulate RAGE expression levels in various tissues and that sRAGE could be mainly generated from proteolytic cleavage of membrane-bound RAGE by the actions of sheddase, a disintegrins and metalloproteinases 10 (ADMA 10) [4,7,8], it is also possible that sRAGE may reflect tissue RAGE expression and the severity of target organ damage. Accordingly, whether sRAGE is a biomarker that could reflect tissue damage or a protective one against injury might differ considerably depending on the patients' background. Indeed, although Falcone et al. reported that low levels of sRAGE were independently associated with the presence of coronary artery disease in non-diabetic men [9], prospective studies have shown that higher levels of sRAGE are associated with incident of cardiovascular disease or all-cause mortality in subjects with either type of diabetes [10–12].

The beneficial effects of statin therapy in reducing cardiovascular pathogenesis, atherosclerosis, and diabetic complications are well known. Although the mechanisms by which statins provide cardiovascular benefits are not fully understood, the regression and stabilization of coronary artery plaque are presumed to play an important role in this effect [13,14]. A recent study has reported that statins stimulate the production of sRAGE [15]. Although atorvastatin has been shown to increase serum sRAGE levels [16], whether modulation of circulating sRAGE levels has a beneficial effect on the progression of atherosclerosis is unknown. In this study, we examined the effects of statins on serum AGEs and sRAGE levels and their association with coronary atherosclerosis.

2. Methods

2.1. Patients and study design

The present study is a post-hoc subanalysis of the Treatment With Statin on Atheroma Regression Evaluated by Intravascular Ultrasound With Virtual Histology (TRUTH) trial. The TRUTH study was a prospective, open-label, randomized, multicenter trial performed at 11 Japanese centers to evaluate the effects of 8 months' treatment with pitavastatin versus pravastatin on coronary atherosclerosis using virtual histology (VH)-intravascular ultrasound (IVUS) [17]. Briefly, 164 patients with angina pectoris were randomized to either pitavastatin (4 mg/day, intensive lipid-lowering) or pravastatin (20 mg/day, moderate lipid-lowering) therapy after successful percutaneous coronary intervention (PCI) performed under VH-IVUS guidance. None of the participants were taking a statin or other lipid-lowering drugs at the time of study enrollment. A follow-up IVUS examination was performed after 8 months of statin therapy.

The inclusion criteria of this study were analyzable IVUS data obtained at PCI and at the 8-month follow-up, along with adequate serum volume in frozen samples for various measurements. A total of 91 patients were included in this study.

The TRUTH study was conducted in accordance with the Declaration of Helsinki and with the approval of the ethical committees of the 11 participating institutions. Each patient enrolled in the study provided written informed consent.

2.2. IVUS examination and analysis

The details of the IVUS procedure have been documented elsewhere [17]. Briefly, after PCI of the culprit lesion, IVUS examination was performed on angiographic lesions without significant stenosis by coronary angiogram (diameter stenosis < 50%). An IVUS catheter (Eagle Eye Gold; Volcano Corporation, San Diego, California) was used, and a motorized pullback device was used to withdraw the transducer at 0.5 mm/s. During pullback, grayscale IVUS was recorded, and raw radiofrequency data were captured at the top of the R wave using a commercially available IVUS console (IVG3; Volcano Corporation). After 8 months of statin therapy, the IVUS examination was repeated in the same coronary artery, using the same type of IVUS catheter that was used at baseline.

All baseline and follow-up IVUS core laboratory analyses were performed by an independent and experienced investigator (M.T.) in a blinded manner. Before IVUS analysis, baseline and follow-up IVUS images were reviewed side-by-side on a display, and the distal and proximal ends of the target segment were identified based on reproducible anatomical landmarks such as the side branch, vein, and stent edge. Plaques close to the PCI site (<5 mm) were excluded because mechanical interventions affected atheroma measurements. Quantitative IVUS grayscale analysis was performed according to the guidelines of the American College of Cardiology and European Society of Cardiology [18]. Manual contour detection of the lumen and external elastic membrane (EEM) was performed for each frame. The EEM volume and lumen volume were calculated, and the difference between the 2 values was defined as plaque volume. All volumetric data were divided by lesion length to obtain a volume index. Intraobserver analysis was carried out in 25 randomly selected lesions from 25 vessels at least 4 weeks apart. The intraobserver variabilities for the EEM volume and lumen volume were 2.5 ± 2.4% and 2.7 ± 2.5%, respectively. VH-IVUS data analysis was based on calculation of grayscale border contour, and the relative and absolute quantities of different coronary artery plaque components were measured using IVUSLab version 2.2 (Volcano Corporation). Fibrous tissue was marked in green, fibro-fatty in yellow, dense calcium in white, and necrotic core in red on the VH-IVUS image [19].

2.3. Blood sampling and measurement of blood parameters

Blood samples were obtained after an overnight fast at baseline and at the 8-month follow-up. The levels of serum lipid and high-sensitivity C-reactive protein (hs-CRP) were measured at a central clinical laboratory (SRL Inc., Tokyo). Serum levels of total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides were measured by standard enzymatic methods. Serum oxidized LDL levels were measured by an enzyme immunoassay. Serum levels of small dense LDL, AGEs, and sRAGE were measured using conserved frozen samples. Serum small dense LDL levels were measured by a homogeneous assay (Denka Seiken Co., Ltd., Tokyo) [20]. Serum AGEs levels were measured by enzyme-linked immunosorbent assay (ELISA), as described previously [21]. sRAGE levels were determined using a commercially available ELISA kit (R&D systems, Minneapolis, Minnesota).

2.4. Statistical analysis

Statistical analysis was performed using StatView version 5.0 (SAS Institute, Cary, North Carolina). Results are expressed as mean ± SD or as median (range). Differences in continuous variables were compared using Student's paired *t* tests when variables showed a normal distribution, and the Wilcoxon signed rank-sum test when the variables were not normally distributed. Univariate and multivariate regression analyses were performed to assess predictors associated with percentage changes in EEM volume and plaque volume after statin therapy. The variables with a p value < 0.2 on univariate analysis were entered into multivariate models. Statistical significance was set at $p < 0.05$.

3. Results

3.1. Patients' characteristics and laboratory results

The patients' baseline characteristics are listed in Table 1. Their mean age was 67 years, and 75 patients (82%) were men. Sixty-six patients (73%) had stable angina pectoris, and the remaining 25 (27%) had

Table 1
Baseline characteristics of subjects.

	All subjects (n = 91)
Age (years)	67 ± 10
Men	75 (82%)
Body mass index (kg/m^2)	24.2 ± 3.4
eGFR (ml/min/1.73 m^2)	64.4 ± 14.4
Status of coronary artery disease	
Stable angina pectoris	66 (73%)
Unstable angina pectoris	25 (27%)
Treatment allocation	
Pitavastatin	46 (51%)
Pravastatin	45 (49%)
Target coronary artery	
Left anterior descending	51 (56%)
Left circumflex	4 (4%)
Right	36 (40%)
Type of stent	
Bare metal stent	15 (16%)
Drug-eluting stent	76 (84%)
Hypertension	60 (66%)
Diabetes mellitus	41 (45%)
Smoking	22 (24%)
Medications	
ACE inhibitors or ARBs	49 (54%)
Beta-blockers	9 (10%)
Calcium channel blockers	50 (55%)

Data are expressed as the mean ± SD or number (%).
eGFR, estimated glomerular filtration rate; ACE, angiotensin-converting enzyme; and ARBs, angiotensin-receptor blockers.

unstable angina pectoris. Forty-six patients (51%) were treated with pitavastatin, and the remaining 45 (49%) received pravastatin.

Risk factor data at baseline and at the 8-month follow-up are shown in Table 2. At the 8-month follow-up, serum levels of total cholesterol, LDL cholesterol, triglycerides, apolipoprotein B, hs-CRP, and small dense LDL had decreased significantly, whereas serum levels of HDL cholesterol and apolipoprotein A1 had increased significantly. Statins had no effects on serum AGEs levels; however, serum levels of sRAGE were significantly higher at the 8-month follow-up.

3.2. Grayscale IVUS and VH-IVUS analysis

The parameters evaluated using grayscale IVUS and VH-IVUS are listed in Table 3. A significant decrease in EEM volume (−1.6%, p = 0.005) was observed, whereas a decrease in plaque volume did not reach statistical significance (−1.9%, p = 0.16). A significant decrease in the fibro-fatty component (−0.28 mm^3/mm, p < 0.0001) and increases in the necrotic core (0.14 mm^3/mm, p = 0.02) and dense calcium components (0.14 mm^3/mm, p < 0.0001) were observed after 8 months' statin therapy.

Table 2
Risk factor control at baseline and at the 8-month follow-up.

	Baseline	Follow-up	p value
Total cholesterol (mg/dl)	203 ± 35	158 ± 27	<0.0001
LDL cholesterol (mg/dl)	130 ± 32	84 ± 25	<0.0001
Triglycerides (mg/dl)	116 (36 to 573)	102 (37 to 360)	0.005
HDL cholesterol (mg/dl)	47 ± 11	51 ± 13	0.0004
Apolipoprotein A1 (mg/dl)	118 ± 20	132 ± 26	<0.0001
Apolipoprotein B (mg/dl)	104 ± 24	74 ± 17	<0.0001
Hs-CRP (ng/ml)	4100 (54 to 88900)	642 (52 to 26200)	<0.0001
Oxidized LDL (U/ml)	12 ± 9	11 ± 9	0.19
Lipoprotein(a) (mg/dl)	16 (1 to 47)	14 (1 to 118)	0.002
Small dense LDL (mg/dl)	26 ± 14	19 ± 9	<0.0001
Glucose (mg/dl)	112 ± 33	108 ± 33	0.046
HbA1c (%)	6.3 ± 1.0	6.2 ± 0.8	0.26
AGEs (U/ml)	11.6 ± 5.7	11.5 ± 4.0	0.93
sRAGE (pg/ml)	974 ± 425	1041 ± 434	0.049

Data are expressed as the mean ± SD or as median (range).
LDL, low-density lipoprotein; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; HbA1c, hemoglobin A1c; AGEs, advanced glycation end-products; and sRAGE, soluble form of receptor for AGEs.

Table 3
The parameters evaluated using grayscale IVUS and VH-IVUS at baseline and at the 8-month follow-up.

	Baseline	Follow-up	p value
EEM volume index (mm^3/mm)	15.94 ± 4.78	15.66 ± 4.75	0.005
% change		−1.6 ± 5.7	
Plaque volume index (mm^3/mm)	8.65 ± 2.60	8.53 ± 2.60	0.16
% change		−1.9 ± 10.5	
Lumen volume index (mm^3/mm)	7.30 ± 2.66	7.13 ± 2.60	0.07
% change		−1.6 ± 11.8	
PAV (%)	54.5 ± 6.4	54.7 ± 6.4	0.65
Nominal change (%)		0.2 ± 4.2	
FI volume index (mm^3/mm)	3.16 ± 1.47	3.08 ± 1.37	0.32
Change (mm^3/mm)		−0.08 ± 0.78	
FF volume index (mm^3/mm)	1.03 ± 0.76	0.75 ± 0.60	<0.0001
Change (mm^3/mm)		−0.28 ± 0.58	
NC volume index (mm^3/mm)	0.71 ± 0.52	0.85 ± 0.53	0.02
Change (mm^3/mm)		0.14 ± 0.54	
DC volume index (mm^3/mm)	0.39 ± 0.32	0.49 ± 0.36	<0.0001
Change (mm^3/mm)		0.14 ± 0.54	
Average length (mm)	25 ± 15	25 ± 15	0.67

Data are expressed as the mean ± SD.
EEM, external elastic membrane; PAV, percent atheroma volume; FI, fibrous; FF, fibro-fatty; NC, necrotic core; and DC, dense calcium.

3.3. Predictors of percentage change in plaque volume after statin therapy

Univariate regression analyses showed that the percentage change in serum sRAGE was negatively correlated with the percentage changes in EEM volume (r = −0.198, p = 0.06) and plaque volume (r = −0.247, p = 0.02) (Fig. 1). Age tended to be positively correlated with the percentage change in plaque volume on univariate regression analysis (Table 4). Multivariate regression analysis showed that an increase in serum sRAGE was an independent negative predictor (β = −0.290, p = 0.006), and age was an independent positive predictor (β = 0.222, p = 0.03) associated with atheroma progression after statin therapy. An increase in serum sRAGE levels did not correlate with the changes in any of the 4 plaque components evaluated by VH-IVUS.

4. Discussion

The major findings of this study are as follows: (1) serum sRAGE levels were elevated after statin therapy following PCI, (2) this increase in serum sRAGE levels was associated with negative vessel remodeling and a regression in plaque volume, but was not correlated with changes in plaque composition; and (3) an increase in serum sRAGE was an independent predictor associated with atheroma regression after statin therapy.

Serum levels of sRAGE are positively rather than inversely correlated with circulating AGEs in both diabetic and non-diabetic subjects [4]. In addition, serum sRAGE levels are significantly higher in diabetic patients than in non-diabetic subjects [22]. Furthermore, serum sRAGE levels were one of the independent determinants of coronary artery disease in patients with diabetes [22]. On the basis of these reports, serum sRAGE levels may reflect tissue RAGE expression and may be elevated as a compensatory mechanism against AGE-elicited tissue damage and circulating sRAGE level is a novel biomarker of vascular inflammation in diabetic patients. However, Falcone et al. reported that low levels of sRAGE were independently associated with the presence of coronary artery disease in non-diabetic men [9]. In addition, Selvin et al. reported that low plasma levels of sRAGE were independently associated with the risk of cardiovascular disease and all-cause mortality in community-based population [23]. These observations suggest that

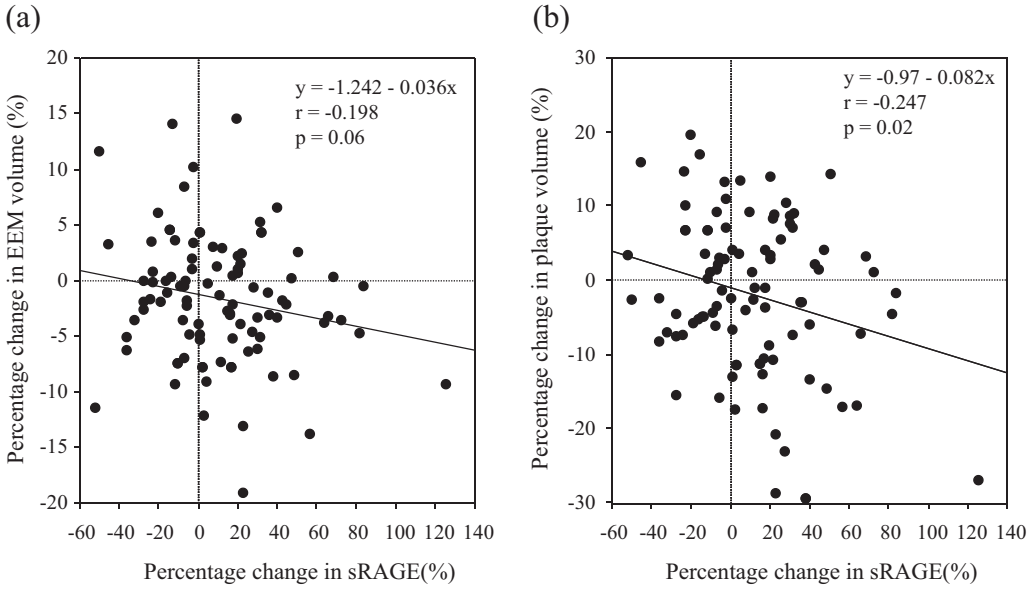

Fig. 1. Correlations between percentage change in serum soluble form of receptor for advanced glycation end products (sRAGE) and percentage change in external elastic membrane (EEM) volume (a) or plaque volume (b) during statin therapy. The percentage change in serum sRAGE was negatively correlated with the percentage changes in EEM volume ($r = -0.198$, $p = 0.06$) and plaque volume ($r = -0.247$, $p = 0.02$) after statin therapy.

clinical significance of sRAGE as a biomarker may differ considerably depending on the patient's background, particularly with or without diabetes [24].

A few studies have evaluated the effect of pharmacotherapies on serum sRAGE levels and there is still some controversy over the therapeutic modulation of sRAGE. Forbes et al. reported that inhibition of the renin–angiotensin system by perindopril, an angiotensin-converting enzyme inhibitor, in patients with type 1 diabetes increased plasma sRAGE levels [25]. Nakamura et al. reported that telmisartan, an angiotensin receptor blocker, decreased serum sRAGE levels in patients with essential hypertension [26]. A recent ex-vivo study reported that statin stimulates the production of sRAGE [15]. In addition, atorvastatin increased serum sRAGE levels [16,27]. Consistently with these reports, in the present study, statin therapy was associated with an increase in serum sRAGE levels. In addition, an increase in serum sRAGE was associated with negative vessel remodeling and atheroma regression in the coronary artery. To the best of our knowledge, this is the first report to evaluate the effect of statins on serum sRAGE levels and its association with changes in coronary atherosclerosis.

Table 4
Predictors of the percentage change in plaque volume after statin therapy.

	Univariate		Multivariate	
	r	p value	β	p value
Age	0.166	0.12	0.222	0.03
Gender	−0.057	0.59		
Coronary artery disease status	−0.024	0.82		
Hypertension	0.106	0.32		
Diabetes mellitus	0.133	0.21		
Smoking	0.104	0.32		
Type of statin	−0.051	0.63		
Total cholesterol (% change)	−0.025	0.81		
LDL cholesterol (% change)	−0.025	0.81		
Triglycerides (% change)	0.061	0.57		
HDL cholesterol (% change)	−0.107	0.31		
Apolipoprotein A1 (% change)	−0.098	0.35		
Apolipoprotein B (% change)	0.012	0.91		
Hs-CRP (% change)	0.087	0.42		
Oxidized LDL (% change)	0.094	0.39		
Lipoprotein(a) (% change)	0.020	0.85		
Small dense LDL (% change)	−0.040	0.71		
Glucose (% change)	−0.026	0.83		
HbA1c (% change)	−0.189	0.26		
AGEs (% change)	−0.063	0.55		
sRAGE (% change)	−0.247	0.02	−0.290	0.006

Male gender, unstable angina pectoris, hypertension, diabetes mellitus, smoking, and pitavastatin were assigned a value of 1. Female gender, stable angina pectoris, normotension, non-smoking, non-diabetes mellitus, and pravastatin were assigned a value of 0.

RAGE is up-regulated in the atherosclerotic plaque in patients with diabetes [28]. In addition, recent studies reported that statin therapy attenuates the accumulation of RAGE in plaque [29,30]. Although we did not evaluate the RAGE expression in plaque, its inhibition following statin therapy could play a role in negative vessel remodeling and atheroma regression in the coronary arteries. Statin therapy decreases matrix metalloproteinase (MMP) activity and increases collagen content in human plaques [31,32], while circulating MMP levels are associated with coronary artery plaque regression [33]. Recently, Cuccurullo et al. reported that RAGE suppression by simvastatin had a protective impact on plaque phenotype, while reduced MMP expression was correlated with an increase in plaque collagen content after statin therapy [30]. These reports suggest that statin therapy stabilizes coronary artery plaques via the suppression of RAGE and MMP expression within the atherosclerotic plaque.

The beneficial effects of statin therapy in reducing cardiovascular pathogenesis, atherosclerosis, and diabetic complications are well known. Of course, these effects of statins are mainly based on the reduction of LDL cholesterol levels. However, the clinical benefits of statins are greater than those expected from their LDL cholesterol-lowering effect alone. Statins are known to have pleiotropic effects, which include reducing CRP and AGEs [34,35]. RAGE is the best known target for AGEs in the vasculature, and it is well established that the AGEs–RAGE system contributes to the progression of atherosclerotic plaque in animal models [6,36,37]. Previous studies reported that atorvastatin decreased serum levels of AGEs in patients with type 2 diabetes or nonalcoholic steatohepatitis, or non-diabetic patients with chronic kidney disease [35,38,39]. However, we did not observe a decrease in serum AGEs levels after statin therapy. sRAGE level is independently and inversely associated with high mobility group box 1 (HMGB1) value in a general population [40]. HMGB1 is one of the ligands for RAGE, and HMGB1 and RAGE interaction promotes chemotaxis and maturation of immune cells, enhances the expression of adhesion molecules, and stimulates

the production of cytokines by various types of cells [4]. HMGB1 level is increased in diabetic RAGE$^{-/-}$/apoE$^{-/-}$ mice, while sRAGE is absent in these animals [40]. Furthermore, HMGB1 has 10 times higher binding affinity to RAGE, and its serum concentration is 1000 times less than that of AGEs [4,40]. These findings suggest that circulating HMGB1 but not AGEs might be a molecular target for sRAGE. An increase in sRAGE levels observed in this study is one of the pleiotropic effects of statins, as previously reported [16,27]. Given the correlations between the increase in serum sRAGE levels and plaque regression or negative vessel remodeling after statin therapy, statin-induced changes in coronary atherosclerosis may be mediated, in part, by the AGEs-RAGE system.

4.1. Limitations

Our study has several limitations. First, although sRAGE may be an important target molecule for preventing the progression of atherosclerosis, this study was a post-hoc subanalysis. In addition, serum sRAGE levels were measured using frozen samples, and we cannot clarify the source of elevated serum sRAGE levels. Furthermore, we neither evaluated the RAGE and MMP expression in plaques nor measured serum MMP and HMGB1 levels. Second, although we excluded patients with angiographically apparent thrombi, an intramural thrombus might have influenced the study results. Third, the IVUS examination was only performed in non-culprit lesions in the culprit vessel. Mechanical interventions might have affected the atheroma measurement. Finally, this study was limited by the relatively small number of patients and had no control subjects who did not take statins during the 8 months following PCI. Larger prospective studies are necessary to confirm the role of sRAGE in the progression or regression of coronary atherosclerosis.

5. Conclusions

Statin therapy after PCI increased serum sRAGE levels and this increase was associated with negative vessel remodeling and atheroma regression in the target coronary artery. Statin-induced changes in coronary atherosclerosis may be mediated, in part, by the AGEs-RAGE system.

Disclosures

None.

Conflict of interest

None.

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