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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

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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

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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