

Original Article

Inverse Association between Circulating Levels of Soluble Receptor for Advanced Glycation End-Products and Coronary Plaque Burden

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Aim: Low levels of soluble receptor for advanced glycation end-products (sRAGE) have been reported to be associated with coronary artery disease (CAD) and peripheral atherosclerosis. This study explored the relationship between circulating levels of sRAGE and the characteristics of coronary vessels detected by 64-slice computed tomography angiography (CTA).

Methods: In this cross-sectional study we included 127 consecutive patients with CAD but without acute coronary syndrome. Quantitative volumetric analysis of the lumen and plaque burden of the vessel wall (soft and calcific components) was performed for the three major coronary vessels. Each component was expressed as a percentage of vessel volume and utilized in per-patient analysis. The patients were classified into two groups according to the presence of calcium volume: non-calcified plaque (NCP) group (calcium volume % = 0) and calcified plaque (CP) group (calcium volume % > 0).

Results: In the NCP group, but not in the CP group, simple regression analysis revealed a negative association of total plaque burden % with sRAGE ($\beta = -0.378$, $p = 0.0019$) and HDL cholesterol ($\beta = -0.368$, $p = 0.003$) and a positive association with creatinine ($\beta = 0.258$, $p = 0.041$) and male gender ($\beta = 0.317$, $p = 0.01$). After adjusting for confounding factors, the total plaque burden % remained significantly associated only with sRAGE ($\beta = -0.358$, $p = 0.011$).

Conclusions: Circulating sRAGE levels are associated in an inverse manner with non-calcified plaque burden, suggesting that it may be related with early atherosclerosis and plaque progression.

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Key words; 64-slice computed tomography angiography, Soluble receptor for advanced glycation end-products, Coronary artery disease

Introduction

The receptor for advanced glycation end-products (RAGE) is a multi-ligand receptor that contributes to the pathogenesis of tissue injury in metabolic disorders and aging through innate and adaptive inflammatory mechanisms¹⁻³.

In recent years, the circulating isoform of RAGE, called soluble RAGE (sRAGE), which is able to competitively inhibit ligand binding to membrane-bound

RAGE, was reported as an emerging biomarker in cardiovascular, metabolic and inflammatory diseases^{4,5}.

sRAGE, consisting of the extracellular ligand-binding domain only, lacking both cytoplasmic and transmembrane domains, is generated by alternative splicing or proteolytic cleavage of full-length RAGE². It circulates in human plasma and is still able to bind ligands and thus antagonize RAGE signalling^{4,5}. This hypothesis is supported by animal testing, where administration of sRAGE to mouse models retarded the progression of atherosclerosis, and by clinical studies, where low sRAGE levels were reported to be linked to the presence of angiographically proven coronary artery disease (CAD)⁶, cardiovascular events⁷ and carotid intima media thickness^{8,9}, suggesting a vascular-protective role for this molecule.

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Multi-slice computed tomography angiography (CTA) is a non-invasive tool that produces high-resolution imaging of the coronary artery wall and allows more reliable detection of both obstructive and non-obstructive subclinical CAD at an earlier stage than by invasive angiography¹⁰⁻¹². CTA permits the detection of both calcified plaque and non-calcified coronary atherosclerotic plaque with good agreement with intravascular ultrasound¹³.

Aim

To assess the relationship between sRAGE plasma levels and the characteristics of coronary vessels detected by CTA in a cohort of subjects who presented with chest pain syndrome and in whom acute coronary syndrome (ACS) had been excluded.

Methods

Study Population

From November 2007 to July 2009 we recruited 200 consecutive patients (age 63.3 ± 12 years; 63.5% men) with chest pain syndrome, proven or suspected CAD who had been screened with 64-slice CTA according to guidelines¹⁴.

The exclusion criteria were as follows: patients who were either suspected of having ACS or had severe symptoms before CTA ($n=10$), patients with chronic total occlusion ($n=13$), elevated pre-procedural cardiac biomarkers ($n=14$), previous stenting ($n=23$), and inestimable-quality CTA imaging ($n=13$). Thus, the final study population was 127 patients.

The study protocol was approved by the institutional ethics committee and all patients provided informed consent to the study.

Cardiovascular Risk Factors

We obtained information on and clinical measurements of risk factors and medication during the patient's visit. Hypertension was defined as systolic blood pressure over 140 and/or diastolic blood pressure over 90 mmHg and/or treatment with antihypertensive medication. Antihypertensive therapy included the following classes of drugs or any combination of them: ACE inhibitors, calcium-antagonists, beta-blockers, and diuretics. Platelet aggregation inhibitors, such as aspirin (< 500 mg/day), were recorded.

Hypercholesterolemia was defined as fasting cholesterol over 200 mg/dL or use of cholesterol-lowering drugs (statins, fibrates, bile acid sequestrants and nicotinic acid derivatives). Diabetes was defined as fasting serum glucose levels over 126 mg/dL or use of antidia-

betic medication (insulin or any oral antidiabetic medication). Subjects were classified as smokers if they had smoked at least one cigarette per day in the year before the study. Information was collected on previous cardiovascular and cerebrovascular events. A family history of CAD was defined as having a first-degree female (< 65 years) or male (< 55 years) relative with a documented history of myocardial infarction (MI), sudden cardiac death and surgical or percutaneous coronary revascularization.

The Framingham risk score was calculated for each subject using the risk score of Wilson *et al.*¹⁵.

Laboratory Assays

Blood samples were drawn before the CTA procedure and collected in tubes without additives, containing heparin or citrate (for routine biochemistry). Total cholesterol, high density lipoprotein (HDL) cholesterol, triglycerides, and glucose were determined using routine laboratory procedures. Plasma and serum samples were centrifuged at 4°C , immediately divided into aliquots and stored at -80°C until analysis. All laboratory determinations were performed in a blinded fashion.

sRAGE Assay

Blood samples were collected in tubes containing Na₂EDTA, and sRAGE levels were determined using a double-sandwich ELISA kit (DuoSet ELISA development kit; R&D Systems, Minneapolis, MN) as described previously⁹. The intra-assay and inter-assay coefficients of variation were 5.9% and 8.2%, respectively. The lower limit of sRAGE detection was 21.5 pg/mL.

64-Slice CTA Scan

The patients underwent 64-slice CTA (Light-Speed VCT 64, GE Healthcare, Milwaukee, WI) with the following scan parameters: retrospective ECG gating; 912 channel detectors along the gantry and 64 channel detectors along the z-axis; tube voltage 120 kV; tube current 350-750 mA (depending on patient size); scan FOV 50 cm; gantry rotation 0.35 s/rotation; matrix 512²-512; slice thickness 0.625 mm; range of helical pitch 0.18-0.24. When appropriate the following premedications were administered: metoprolol, up to 5 mg intravenously, to lower the heart rate below 65 beats per minute; isosorbide dinitrate, up to 1 mg intravenously, to guarantee maximal epicardial vasodilatation. Non-ionic iodinated contrast medium (Iomeprol 400; Bracco Imaging SpA, Milan, Italy) was injected via a peripheral vein according to a triphasic protocol using a programmable injector

(Nemoto Dual Shot Injector; Nemoto Kyorindo Co. Ltd., Tokyo, Japan) with a two-way syringe system: in the first phase, rapid injection of contrast medium (from 5 to 8 mL/sec) was performed; in the second phase, 10 mL contrast at 1 mL/sec was injected simultaneously with 25 mL saline at 2.5 mL/sec; in the third phase, 35 mL saline flush was administered at 4 mL/sec (maximal total volume of contrast medium 110 mL). To time the scan, a region of interest (ROI) was placed in the right ventricular cavity to detect peak enhancement. Scans were performed during breath hold; patients were monitored continuously through single-lead electrocardiography. The scan parameters were programmed in order to limit radiation exposure to 15 mSv on average. After the procedure, patients had an intravenous infusion of saline (500 mL) to improve hydration and prevent contrast-induced nephropathy. Moreover, all patients were instructed to repeat the measurement of serum creatinine between 2 and 7 days after the examination.

Image Reconstruction and Analysis

Trans-axial CT images were reconstructed using a slice thickness of 0.625-mm and 0.4-mm increments. The data were then transferred to a dedicated workstation (Advantage Workstation 4.3; GE Healthcare) for post-processing. Lumen size (diameter and area) of the major coronary arteries was measured using "Multiplanar Reformatting Images" reconstruction with an automatic interactive program. Lumen reduction $\geq 50\%$ was classified as significant stenosis. Volumetric analysis of the coronary vessel wall was evaluated using Color Code Plaque analysis software (GE Healthcare)¹⁶. This densitometric method, based on the Hounsfield scale, allows the computation of a cylindrical volume around the vessel lumen and the relative contribution of calcium, fibro-fatty and fibromuscular components of the vessel wall. The algorithm of vessel wall analysis was tuned in each patient according to densitometric parameters measured by a ROI on the aortic root, left ventricular myocardium and epicardial fat. Using this system, CT density < 60 HU was attributed to the fibro-fatty component, between 60 and 200 HU to the fibro-muscular component, while calcified plaques were differentiated from the lumen when they had a density > 800 HU. The program output gave a quantitative volumetric measurement (mm^3) of each component. In this paper we considered the total plaque burden as the sum of the soft component (defined as fibro-fatty and fibrotic component) and calcified component in the three major coronary vessels. Each component was also expressed as a percentage of vessel volume and utilized

in per-patient analyses.

Statistical Analysis

Data were analyzed with the use of statistical software SPSS 13.0 (SPSS Inc., Chicago, IL).

The Kolmogorov-Smirnov test of normality was used to verify whether the distribution of variables followed a Gaussian pattern. Data with a normal distribution are given as the mean \pm SD. Variables with a skewed distribution are expressed as the median and interquartile range. Group differences were analyzed by Student's *t*-test, and the χ^2 test for normally distributed and non-continuous variables, respectively. Variables with a non-normal distribution were logarithmically transformed before each analysis.

Simple regression analysis and multivariate linear regression analysis were used to test the relationship among clinical, laboratory, and CTA parameters. Traditional risk factors and factors with $p < 0.10$ on univariate analysis were entered into multiple regression analysis. A two-tailed *p*-value < 0.05 was considered significant.

Results

A total of 381 major coronary vessels were evaluated in 127 patients. Coronary calcification (calcium volume) was tallied in mm^3 by CTA analysis, and the patients were stratified into two groups by their calcium volume percentage [(calcium volume/vessel volume)*100]: the non-calcified plaque (NCP) group (calcium volume % = 0) and the calcified plaque (CP) group (calcium volume % > 0). Subject characteristics of the two groups are summarized in **Table 1**. Patients in the CP group, compared with those in the NCP group, were prevalently male ($p = 0.006$), significantly older ($p = 0.0002$) and had a higher Framingham Risk Score ($p < 0.0001$). Moreover they had a higher prevalence of hypertension ($p < 0.0001$), previous myocardial infarction ($p = 0.02$), stenosis $\geq 50\%$ in at least one coronary artery segment ($p < 0.0001$), hyperlipidemia ($p = 0.001$) and a lower prevalence of smoking ($p = 0.03$).

As shown in **Table 2**, measurements of vessel (wall plus lumen) and lumen volume did not differ between NCP and CP groups; however, in the CP group, patients with at least one-vessel stenosis $\geq 50\%$ had a total lumen volume % significantly lower than in patients without stenosis (56.6 ± 11 vs 61.2 ± 12 , $p = 0.049$), while a significantly higher total plaque volume % (43.12 ± 11.1 vs 38.3 ± 12 , $p = 0.048$) (**Table 2**). As expected, all patients with stenosis $\geq 50\%$ ($n = 46$) had a total plaque burden % more elevated than

Table 1. Demographic and clinical characteristics of the study population

	NCP group (n=65)	CP group (n=62)	p value
Age (yrs)	58.9 ± 11.9	66.6 ± 10.7	0.0002
Men, n (%)	34 (52)	47 (76)	0.006
BMI, kg/m ²	26.9 ± 4	26.6 ± 2.9	0.66
Hypertension, n (%)	11 (17)	39 (63)	<0.0001
Diabetes mellitus, n (%)	6 (9)	10 (16)	0.24
Hyperlipidemia, n (%)	16 (25)	33 (53)	0.001
Smoking, n (%)	16 (25)	6 (10)	0.03
Family history of CAD, n (%)	41 (63)	38 (61)	0.83
Previous myocardial infarction, n (%)	2 (3)	9 (14)	0.02
Stenosis ≥ 50%, n (%)	8 (12)	38 (61)	<0.0001
Framingham risk score	9.65 (5.2-17.34)	16.15 (12.1-24.18)	<0.0001
Laboratory profile			
Glucose (mg/dL)	106.8 ± 20.7	100.8 ± 24.9	0.37
Cholesterol (mg/dL)	197.4 ± 46.5	187 ± 42	0.22
LDL Cholesterol (mg/dL)	126 ± 39.7	119.8 ± 43.8	0.41
HDL Cholesterol (mg/dL)	46.3 ± 14.2	46.4 ± 14	0.97
Triglycerides (mg/dL)	124 (90-150)	106 (83.5-140)	0.75
Creatinine (mg/dL)	0.9 (0.8-1.09)	0.99 (0.8-1.15)	0.48
sRAGE (pg/mL)	1115 (786-1422)	1038 (860-1217)	0.95

Data are given as mean ± SD, number (%) or median (interquartile range). NCP group: non-calcified plaque group; CP group: calcified plaque group; BMI=body mass index; CAD=coronary artery disease; LDL=low density lipoprotein; HDL=high density lipoprotein; sRAGE=soluble receptor for advanced glycation end-products.

Table 2. Vessel characteristics

	NCP group			CP group		
	Total patients (n=65)	Stenosis ≥ 50% (n=8)	No Stenosis ≥ 50% (n=57)	Total patients (n=62)	Stenosis ≥ 50% (n=38)	No Stenosis ≥ 50% (n=24)
Vessel volume (mm ³)	5235 (4041-6393)	4513 (3205-5168)	5257 (4139-6706)	5172 (3930-6211)	5180 (3694-6526)	5129 (4270-6057)
Total lumen volume (mm ³)	2959 (2516-3978)	2676 (1748-2963)	3094 (2552-4146)	2691 (2388-3772)	2672 (2250-3741)	3025 (2470-3786)
Total plaque volume (mm ³)	2000 (1485-2490)	1979 (1093-2205)	2059 (1505-2602)	2166 (1475-2920)	2381 (1513-3006)	2054 (1356-2433)
Total lumen volume (%)	59.9 ± 9.6	56.6 ± 8.99	60.4 ± 9.6	58.3 ± 11.6	56.6 ± 11	61.2 ± 12*
Total plaque volume (%)	39.6 ± 9.5	42.8 ± 9.1	39.1 ± 9.5	41.3 ± 11.6	43.12 ± 11.1	38.3 ± 12**

NCP group: non-calcified plaque group; CP group: calcified plaque group. Data are given as mean ± SD or median (interquartile range).

* $p=0.049$, ** $p=0.048$ between patients with stenosis ≥ 50% and patients without stenosis ≥ 50%.

patients without stenosis (43.0 ± 10.7 vs 38.9 ± 10.3 , $p=0.032$) while they had a total lumen volume % lower than patients without stenosis (56.5 ± 10.7 vs 60.6 ± 10.3 , $p=0.036$).

Using univariate linear regression analysis, in the whole study population, the plaque burden was

inversely associated with plasma levels of sRAGE ($\beta = -0.201$, $p=0.02$) and HDL cholesterol ($\beta = -0.287$, $p=0.014$), while it was positively associated with male gender ($\beta = 0.264$, $p=0.0027$), hyperlipidemia ($\beta = 0.271$, $p=0.0025$) and creatinine (**Table 3**). Regression analysis, performed in two separate groups,

Table 3. Simple regression analysis with percentage of plaque burden as dependent variable

	All patients (<i>n</i> =127)		NCP group (<i>n</i> =65)		CP group (<i>n</i> =62)	
	β	<i>p</i> value	β	<i>p</i> value	β	<i>p</i> value
Age	-0.053	0.55	-0.122	0.33	-0.049	0.702
Male	0.264	0.0026	0.317	0.01	0.198	0.124
BMI	0.134	0.14	0.026	0.84	0.28	0.029
Hypertension	0.076	0.403	-0.046	0.72	0.105	0.42
Diabetes mellitus	0.095	0.286	0.196	0.118	0.015	0.909
Hyperlipidemia	0.271	0.0025	0.237	0.064	0.292	0.022
Smoking	-0.043	0.63	0.013	0.915	-0.082	0.529
Family history of CAD	-0.032	0.72	-0.12	0.340	0.045	0.730
Anti-thrombotic therapy	-0.004	0.96	-0.127	0.998	0.088	0.49
Creatinine	0.200	0.027	0.26	0.041	0.150	0.26
HDL Cholesterol	-0.287	0.0013	-0.368	0.003	-0.223	0.087
sRAGE	-0.201	0.02	-0.378	0.0019	-0.034	0.794

NCP group: non-calcified plaque group; CP group: calcified plaque group.

Table 4. Multiple regression analysis with percentage of plaque burden as dependent variable

	All patients (<i>n</i> =127)		NCP group (<i>n</i> =65)		CP group (<i>n</i> =62)	
	β	<i>p</i> value	β	<i>p</i> value	β	<i>p</i> value
Age	0.064	0.582	0.061	0.717	-0.047	0.78
Male	0.179	0.100	0.216	0.200	0.101	0.55
BMI	0.028	0.762	-0.141	0.293	0.279	0.068
Hypertension	-0.054	0.603	-0.111	0.439	0.105	0.51
Diabetes mellitus	0.053	0.568	0.051	0.709	-0.21	0.88
Hyperlipidemia	0.223	0.032	0.207	0.165	0.234	0.13
Smoking	-0.112	0.25	-0.141	0.293	-0.33	0.83
Family history of CAD	0.006	0.95	0.003	0.979	-0.012	0.94
Anti-thrombotic therapy	-0.103	0.32	-0.242	0.111	0.0002	0.998
Creatinine	0.145	0.118	0.087	0.508	0.077	0.604
HDL Cholesterol	-0.123	0.274	-0.136	0.457	-0.169	0.324
sRAGE	-0.149	0.106	-0.358	0.0115	0.013	0.930

NCP group: non-calcified plaque group; CP group: calcified plaque group.

revealed an inverse association between total plaque burden and both sRAGE levels ($\beta = -0.378$, $p = 0.0019$) and HDL cholesterol ($\beta = -0.368$, $p = 0.003$) only in the NCP group (**Table 3**). In addition, in the NCP group, the percentage of total plaque burden was directly associated with creatinine ($\beta = 0.258$, $p = 0.041$) and with male gender ($\beta = 0.317$, $p = 0.01$) (**Table 3**). In the CP group, the percentage of total plaque burden was significantly associated with BMI ($\beta = 0.284$, $p = 0.03$) and hyperlipidemia ($\beta = 0.292$, $p = 0.02$). Multivariate linear regression analysis showed that in the NCP group, the total plaque burden remained only significantly associated

with sRAGE after adjusting for confounding factors and pre-defined variables (**Table 4**).

Regarding the association between sRAGE and the variables indicated in **Table 1**, we found a positive association only with HDL cholesterol ($\beta = 0.336$, $p = 0.0073$) in the NCP group (**Fig. 1**), while no association between sRAGE and diabetes presence was found either in the entire population of the study or in the two separate groups (data not shown). The lack of association between sRAGE levels and diabetes may be due to the low prevalence of diabetics in the enrolled population (12.5%) and to the anti-diabetic treatments.

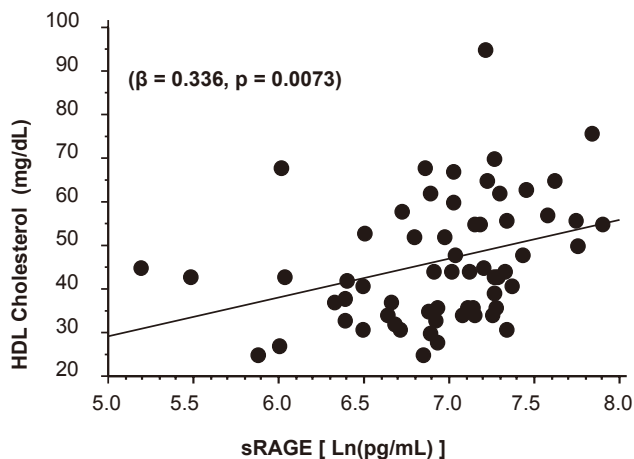


Fig. 1. Correlation between sRAGE and HDL cholesterol levels in NCP group.

Discussion

Our study was designed to examine the relationship of sRAGE with plaque composition and plaque burden through non-invasive CTA assessment. We found that sRAGE plasma levels were inversely associated with total plaque burden in all patients and remained strongly associated in the sub-group of patients without coronary calcification after adjusting for confounding variables. Although previous studies have shown an independent association between low levels of sRAGE and the presence of CAD^{6,7}, this is the first study that shows an inverse association between sRAGE and both coronary atherosclerotic plaque burden and composition detected by CTA. This association is relevant because it is mainly significant in patients with NCP, suggesting a role of sRAGE in the early pathogenesis of atherosclerosis and possibly in the progression and vulnerability of coronary atherosclerotic plaque^{17,18}. Although the exact mechanism of the inverse association between sRAGE and plaque burden remains to be determined, we believe that this biomarker may provide useful information on plaque activity or, better still, of ligand-RAGE hyperactivity associated with the vascular disease state. In other words, the balance among the levels of RAGE ligands, cell-surface RAGE and sRAGE may represent a complex dynamic system and the down-regulation of this latter and the up-regulation of both tissue RAGE and RAGE ligands could have important consequences for the function of endothelial cells, monocytes, macrophages, smooth muscle cells and platelets, thus modulating the initiation and progression of atherosclerosis.

Vascular calcification is age-dependent and is a regulated/active process which could depend also on the ligand-RAGE axis¹⁹. The Dallas Heart Study (2571 subjects, mean age 44 ± 10 years), reported an inverse graded association between sRAGE quartiles and coronary artery calcium (by electron-beam CT)²⁰. Instead, in our study, we found no association between sRAGE and calcium volume (data not shown). This discrepancy could be due to the fact that our patients were older (66.6 ± 10.7 versus 44 ± 10 years) and had a higher degree of CAD severity and calcification than the Dallas Heart Study population. Therefore the association between sRAGE and plaque burden and/or calcification would seem to be lacking in elderly patients with advanced atherosclerotic plaques, characterized by extensive calcification. At this stage of atherosclerosis the inflammatory processes involving the RAGE-ligand axis and sRAGE should be shut down. Hence, we can assume that sRAGE is promising as a potential therapeutic target for the treatment and prevention of atherosclerosis.

We found also a positive correlation between sRAGE and HDL cholesterol in the NCP group. We are unable to explain the significance of this relationship but it could suggest a potential link between sRAGE and HDL metabolism.

Our study has some limitations. This is a cross-sectional study, which limits causal inferences. Also, single measurements of sRAGE and CTA might not be representative of changes in levels over time. In addition, the ELISA kit used detects the total soluble pool of sRAGE and does not distinguish between different sRAGE isoforms. Another limitation is that we measured coronary calcium content from CTA. The presence of contrast medium in CTA images forces reduction of the window of HU for calcium recognition, causing an underestimation of calcium volume. However, data from our laboratory showed a strong correlation between coronary calcium content measured with the standard calcium scoring method without contrast medium and CTA images ($Y = 1.47 + 0.128 * X$; $R^2 = 0.874$, $F = 660.6$, $p < 0.00001$). Avoiding dedicated CT acquisition for calcium scoring before the angiographic studies allowed about 10% sparing of the radiation dose.

Conclusion

In conclusion, this survey of CAD patients shows that circulating sRAGE levels are associated in an inverse manner with coronary plaque burden in patients without calcifications. These findings are compatible with the hypothesis that high sRAGE may

act early as a vasculo-protective factor in this population. Longitudinal observations and intervention studies are warranted to establish whether this link is causal in nature.

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Conflict of Interest

No.

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