Association Between Circulating Soluble Receptor for Advanced Glycation End Products and Atherosclerosis

Observations from the Dallas Heart Study

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OBJECTIVE — To determine the association between circulating soluble receptor for advanced glycation end products (sRAGE) and coronary atherosclerosis.

RESEARCH DESIGN AND METHODS — Using data from the Dallas Heart Study, a probability-based population sample, the association between plasma levels of sRAGE and coronary artery calcium (CAC) was assessed among 2,571 subjects with complete imaging and sRAGE data.

RESULTS — An inverse graded association was observed between sRAGE quartiles and CAC, with CAC prevalence of 28.5% in quartile 1 compared with 15.7% in quartile 4 ($P < 0.0001$). After multivariable adjustment, the associations between sRAGE levels in the first and second quartiles (versus fourth quartile) and CAC remained statistically significant (adjusted odds ratio 1.71 [95% CI 1.2–2.4] and 1.5 [1.0–2.1], respectively).

CONCLUSIONS — sRAGE is a novel biomarker that is inversely associated with coronary atherosclerosis. The role of sRAGE in the pathobiology of atherosclerosis and its potential prognostic and therapeutic implications warrant further investigation.

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The transmembrane receptor for advanced glycation end products (RAGE), expressed on a variety of cells including endothelial, smooth muscle, and mononuclear cells, binds advanced glycation end products and other proinflammatory ligands and modulates activity of several prothrombotic and proinflammatory mediators (1,2). Results from animal models provide evidence supporting a role for ligand-RAGE binding in the development and progression of atherosclerosis (3–5).

A circulating isoform of RAGE, soluble RAGE (sRAGE), has been identified (6,7) and theorized to competitively inhibit transmembrane RAGE-ligand binding, thereby attenuating atherosclerosis (3–5). This hypothesis has been supported by animal experiments, where administration of sRAGE to mouse models retarded the progression of atherosclerosis (3–5).

Few human studies have been performed evaluating the association between circulating sRAGE and human atherosclerosis (8,9). The objective of the present study was to determine the association between sRAGE and atherosclerosis.

RESEARCH DESIGN AND METHODS

— The Dallas Heart Study is a probability-based population sample of adults living in Dallas County with intentional oversampling of black subjects. A detailed study design and variable definitions have previously been published (10); subjects were recruited from July 2000 to January 2002. The present study comprises 2,571 subjects with complete sRAGE and coronary artery calcium (CAC) data. Cardiac electron-beam computed tomography scanning was performed using an Imatron C-150XP scanner with 3-mm slices; duplicate scans were performed within 2 min. The Agatston method was used to determine CAC scores and recorded them as the average of the two scans. Because of skewness, CAC was analyzed as a categorical variable, with prevalent CAC defined by a score >10, a data-derived threshold that optimizes the signal-to-noise ratio to minimize false-positive rates (11).

Venous blood was collected into EDTA tubes and centrifuged for 1,430*g* for 15 min at 4°C. The plasma component was stored at −80°C. Immunoassays for sRAGE were performed in 384-well microtiter plates on thawed frozen plasma samples at Biosite (San Diego, CA). The sRAGE assay was a sandwich ELISA with a minimum detection limit of 0.11 ng/ml. Intra- and interassay coefficients of variation ranged from 6.4 to 8.3% at sRAGE levels of 1.2 and 31.2 ng/ml, respectively. For analyses, subjects were divided into quartiles of sRAGE. Univariable and multivariable logistic regression analyses, with adjustment for traditional atherosclerosis risk factors, were performed to determine associations between sRAGE quartiles and CAC; additional analyses were performed evaluating sRAGE as a continuous variable using a logarithmic transformation of sRAGE levels. Crude and adjusted odds ratios are presented with 95% CIs. Probability values of <0.05 were considered statistically significant. The study protocol was approved by the University of Texas Southwestern Medical Center institutional review board. All participants provided written informed consent.

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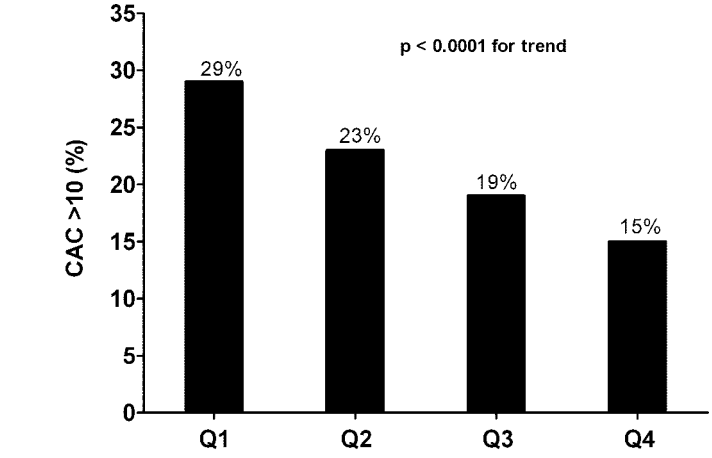

	Q1	Q2	Q3	Q4
N (total=2571)	642	643	643	643
Unadjusted OR	2.2	1.7	1.2	—
Adjusted OR	1.7	1.5	1.2	—
95% CI	1.2-2.4	1.0-2.1	0.9-1.8	
p-value	0.003	0.03	0.22	

Figure 1—*CAC prevalence with unadjusted and adjusted odds ratios (OR) by sRAGE quartile (Q). *Adjusted for age, sex, race, current smoking, diabetes, hypertension, total cholesterol, low HDL cholesterol, and triglycerides.*

RESULTS — The mean age was 44 ± 10 years, with 69% nonwhite subjects and 56% women. Levels of sRAGE were inversely associated with a number of risk factors, including increasing age, diabetes, hypertension, smoking, and metabolic syndrome; compared with white and Hispanic subjects, blacks had significantly lower median sRAGE values.

There was a graded, stepwise, inverse association between CAC prevalence and increasing quartile of sRAGE, from 28.7% in the first quartile (lowest sRAGE levels) to 15.4% in the fourth quartile ($P < 0.0001$; Fig. 1). In multivariable analyses, an independent association remained between an sRAGE values in quartiles 1 and 2 compared with values in quartile 4 (Fig. 1). Analyzed as a continuous variable using log-transformation of sRAGE, the association with CAC remained statistically significant in a multivariable model.

The inverse associations between sRAGE and prevalent CAC were qualitatively similar across selected subgroups stratified by diabetes status, metabolic syndrome status, and race (data not shown).

CONCLUSIONS — The principal novel observation of the present study is that lower levels of sRAGE are independently associated with a greater prevalence of coronary atherosclerosis, demonstrated in a large probability-based population study. These associations remained statistically significant after multivariable adjustment and were evident in the overall population as well as across several key subgroups. Because of small sample sizes in some subsets, validation of the findings in additional studies is needed in key subgroups, including those with diabetes.

Our observations are concordant with the limited data investigating the relationship between circulating sRAGE and atherosclerosis (8,9). In a small cohort of nondiabetic Italian men, Falcone et al. (8) demonstrated that subjects with angiographic coronary artery disease had lower levels of sRAGE than age-matched control subjects without coronary artery disease. Also, Koyama et al. (9) showed that sRAGE was inversely associated with carotid intima-medial thickness. Although both studies are provocative, they are limited by small sample sizes and the discrete populations studied. These reports coupled with the present results provide compelling support for a possible link between sRAGE and atherosclerosis.

Indeed, our observations lend validation to prior experimental observations supporting the plausible contribution of sRAGE to the development and progression of atherosclerosis (3,4). These concordant observations are promising and should prompt further evaluation of the sRAGE/RAGE pathway to better understand the pathobiology and to explore the potential of this pathway as a novel target for the prevention and treatment of vascular disease. The cross-sectional design of our study allows only a demonstration of association, and conclusions cannot be drawn regarding causality. However, evidence from several elegant animal studies demonstrates that exogenous administration of sRAGE suppresses the progression of atherosclerosis (3–5). Therefore, either exogenous administration of sRAGE or therapies that amplify endogenous sRAGE levels may offer an attractive pathway to treat or prevent vascular disease (12). Future investigation into sRAGE modulation as a therapeutic modality is needed.

In summary, within a large multiethnic population, we observed an independent and graded association between lower sRAGE levels and coronary atherosclerosis; therefore, sRAGE could prove to be a useful biomarker for the prediction of atherosclerosis and cardiovascular disease risk. External validation of our data in other populations, especially in cohorts with cardiovascular outcomes, is crucial. With the data from prior basic science experiments and our hypothesis-generating data, sRAGE appears to hold promise not only as a biomarker for atherosclerosis prediction but also as a potential therapeutic target for the treatment and prevention of atherosclerosis and should be investigated further.

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