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Differential Associations between Soluble Cellular Adhesion Molecules and Atherosclerosis in the Dallas Heart Study: a Distinct Role for Soluble Endothelial Cell-Selective Adhesion Molecule

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Abstract

Objective—Endothelial cell-selective adhesion molecule (ESAM) is a junctional-type cellular adhesion molecule (CAM) that is uniquely expressed in vascular endothelium and activated platelets and mediates neutrophil and monocyte diapedesis across the endothelium. Given its role in endothelial pathobiology, we hypothesized that soluble ESAM (sESAM) would be independently associated with atherosclerosis and vascular stiffness.

Methods and Results—We measured sESAM, soluble intercellular adhesion molecule (sICAM)-1 and soluble vascular cell adhesion molecule (sVCAM)-1 in 3222 subjects participating in the Dallas Heart Study, a probability-based population sample. Coronary artery calcium (CAC) was measured by electron beam computed tomography, and abdominal aortic wall thickness (AWT), aortic plaque burden (APB), and aortic compliance (AC) by magnetic resonance imaging (MRI). Increasing levels of sESAM were associated with all major cardiovascular risk factors as well as with inflammatory markers such as monocyte chemoattractant protein-1, but only weakly correlated with sICAM-1 and sVCAM-1. In multivariate analyses, sESAM was independently associated with prevalent CAC (OR 1.2 per SD increase, 95% CI 1.1–1.3; p=0.005), AWT (p=0.035), and AC (p=0.006), but not APB (p=0.15). In contrast, no independent associations were observed between sICAM-1 or sVCAM-1 and any of the atherosclerosis phenotypes.

Conclusions—In this first reported clinical study of sESAM in humans, sESAM levels were independently associated with CAC, AWT, and AC, while sICAM-1 and sVCAM-1 were not. These findings support a unique role of this cellular adhesion molecule in atherosclerosis and suggest the need for further exploration of sESAM as a predictive biomarker and potential mediator of atherosclerosis.

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Keywords

Inflammation; Adhesion molecules; Atherosclerosis; Aortic compliance; Coronary calcium; Biomarkers

Recruitment and migration of leukocytes across the vascular endothelium plays a crucial role in atherosclerotic plaque formation and progression. Several types of molecules facilitate this process and have been associated with atherosclerosis, including P-selectin,[1] intercellular-cell adhesion molecule-1 (ICAM-1),[2–4] vascular cell adhesion molecule-1 (VCAM-1),[2–4] and platelet endothelial cell adhesion molecule-1 (PECAM-1).[5]

Endothelial cell-selective adhesion molecule (ESAM), a recently discovered member of the immunoglobulin superfamily class of cellular adhesion molecules (CAMs), has been specifically localized to endothelial cell tight junctions and activated platelets[6, 7] and is involved in leukocyte migration across vascular endothelium.[8] Because ESAM, like other CAMs, helps regulate leukocyte diapedesis at sites of vascular injury or inflammation, it may play a role in atherosclerotic plaque development and progression. Preliminary data from mice with targeted deletion of ESAM support an important role for ESAM in macrophage infiltration and plaque development, although the exact binding ligands for ESAM have not been determined.[9] Prior studies evaluating the associations between soluble ICAM-1 (sICAM-1) and soluble VCAM-1 (sVCAM-1) with coronary heart disease (CHD) have yielded discordant results;[10] however, among the CAMs, ESAM is uniquely localized to endothelial tight junctions and may be more specifically involved in leukocyte adhesion and transmigration across the endothelium into areas of atherosclerotic plaque formation and progression.

We hypothesized that increased levels of soluble ESAM (sESAM) would be associated with atherosclerosis, based on the putative role of sESAM in mediating endothelial damage attributable to chronic inflammation. To evaluate this hypothesis, we explored independent associations between sESAM and atherosclerosis in the Dallas Heart Study, and contrasted findings with those for two more extensively studied soluble CAMs, sICAM-1 and sVCAM-1.

Methods

Study Population

The Dallas Heart Study (DHS) is a probability-based sample of 6101 Dallas County residents, with intentional over-sampling of self-identified African-Americans and women (final cohort: ~50% African-American and 50% women).[11] The present study is based on the 3222 subjects from the DHS aged 30 to 65 years who had sESAM measured. This study was approved by the Institutional Review Board of the University of Texas Southwestern Medical Center and conducted in accordance with institutional guidelines; all participants provided written informed consent.

Risk factor measurements

Demographic information, anthropometric measurements, and other variable definitions have been described in detail previously.[11] Hypercholesterolemia was defined as a calculated low-density lipoprotein (LDL) cholesterol ≥ 160 mg/dl on a fasting sample, direct LDL ≥ 160 mg/dl on a non-fasting sample, total cholesterol ≥ 240 mg/dl, or use of statin medication.

Hypertriglyceridemia was defined as a fasting triglyceride concentration ≥ 200 mg/dl. Low HDL was defined as HDL-C < 40 mg/dl in men and < 50mg/dl in women. Hypertension was defined as an average systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg or use of antihypertensive medication. Diabetes was defined by a fasting glucose level ≥

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126 mg/dl; or non-fasting glucose of > 200mg/dl; or self-reported diabetes coupled with the use of any glucose lowering medication. Body mass index (BMI) was calculated based on measured height and weight; waist and hip circumference were measured directly at the time of cardiac imaging. Insulin sensitivity was estimated using the homeostasis model assessment (HOMA-IR) calculated using the HOMA Calculator version 2.2.[12]

Atherosclerosis Imaging

Coronary artery calcium (CAC) was measured by the average of two electron beam computed tomography (EBCT) measurements, with prevalent CAC defined by an average score of > 10 Agatston units, a data derived threshold determined to maximize signal to noise ratio, as previously described.[13] Abdominal magnetic resonance imaging (MRI) was performed using a 1.5 Tesla whole-body MRI system (Intera, Philips Medical Systems, Best, The Netherlands). Six transverse slices of the infrarenal abdominal aorta were obtained using a free-breathing, ECG-gated, T2-weighted turbo spin-echo (black-blood) sequence as described previously.[14] Images were analyzed by trained observers blinded to all subject data using the Magnetic Resonance Analytical Software Systems (MASS) cardiac analysis software package (Version 4.2 beta, Medis Medical Imaging Systems, Inc). Atherosclerotic plaque (AP) was identified as hyper-intense signal volume that protruded ≥ 1mm from the endoluminal surface of the aortic wall as previously defined.[15] Plaque was manually contoured in each image, and voxel summation was used to calculate the following endpoints: total vascular area (TVA) = Σ vessel area in each slice for all slices; total plaque area (TPA) = Σ plaque area in each slice for all slices; and aortic plaque burden (APB) = 100 × (TPA / TVA). AWT was calculated by dividing the total vessel wall area by the aortic circumference in each slice. The mean AWT for each participant was determined adding the values of AWT for each slice, and dividing the result by the number of slices. For AC, a high-resolution gradient-echo pulse sequence with a velocity-encoding gradient was applied to obtain an 8 mm axial slice at the level of the pulmonary bifurcation. Aortic cross-sectional area (A_oCSA) was measured on the axial images using the QFLOW® software package (Version 4.1.6, Medis Medical Imaging Systems, Inc). Aortic slice volume (A_oSV) was then calculated as the A_oCSA multiplied by the aortic slice thickness. Blood pressure measurements were obtained with an automated Welch-Allyn arm-cuff sphygmomanometer in the MRI system at the time of imaging from which pulse pressure was calculated (ΔPP = systolic blood pressure – diastolic blood pressure). AC (ml/mmHg) was then calculated as (maximum A_oSV – minimum A_oSV)/ΔPP.

Measurement of sESAM and other biomarkers

Venous blood was collected in standard blood collection tubes containing citrate EDTA and samples were maintained at 4° C for ≤ 4 hours and then centrifuged (1430g for 15 minutes) at 4° C. Plasma was then removed and frozen at −80° C until assays were performed. Risk factors were ascertained within several weeks of blood collection and at the same time as atherosclerosis imaging. All blood-based biomarkers were measured from the same sample. sESAM, sICAM-1, and sVCAM-1 were measured from thawed frozen plasma at Biosite, Inc. (an Inverness Medical Company, Waltham, MA). sICAM-1 and sVCAM-1 were measured using a competitive assay on a Luminex 200 reader (Austin, TX) and modified paramagnetic Luminex beads from Radix Biosolutions (Georgetown, TX) (sICAM-1: minimum detection limit 100 ng/ml; within-assay CV 16%; sVCAM-1: minimum detection limit 200 ng/ml; within-assay CV 17%). sESAM was measured on a proprietary device platform (minimum detection limit 0.25 ng/ml; within-assay CV 13%). Assays were performed by individuals blinded to all clinical data. Samples had been thawed once for aliquoting prior to biomarker measurement.

The following analytes were measured previously and the methods have been described: highsensitivity C-reactive protein (hsCRP),[16] N-terminal pro-B-type natriuretic peptide (NT-

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proBNP) and fructosamine (Roche Diagnostics, Indianapolis, IN);[17] monocyte chemoattractant protein (MCP)-1;[18] soluble CD40 ligand (sCD40L; Bender MedSystems);[19] interleukin-18;[20] osteoprotegerin;[21] leptin; [22] and cystatin C.[23]

The rs5491 single nucleotide polymorphism (SNP) in the ICAM-1 gene has been reported to interfere with the detection of sICAM-1 in African-Americans using an ELISA system (R&D, Minnesota, MN).[24] To determine whether this SNP also interfered with the assay used in the present study, genotyping for the rs5491 SNP was performed using a fluoregenic 5'-nucleotide Taqman assay system (Applied Biosystems) performed on a HT7900 Real-Time PCR system.[25]

Statistical Analysis

All statistical analyses were performed using SAS Version 9.1.3 (Cary, NC, USA). For all atherosclerosis phenotypes, sESAM, sICAM-1, and sVCAM-1 were analyzed in unadjusted and adjusted models (Model 1: including age, sex, race, hypertension, diabetes, current smoking, hypercholesterolemia, hypertriglyceridemia, low HDL-C, and BMI; Model 2: Model 1 plus sESAM, sICAM-1 and sVCAM-1; Model 3: Model 2 plus MCP-1 and hsCRP). sESAM was normally distributed. sICAM-1 and sVCAM-1 required log transformation for all regression models to meet assumptions of linearity. Logistic regression models were performed to assess associations with CAC score > 10 and aortic plaque prevalence (AP). Odds ratios were calculated for one standard deviation change in sESAM, sICAM-1, and sVCAM-1. Multivariable linear regression was performed to evaluate associations with AWT, AC, and APB with similar variables as in the logistic regression models. Because the continuous measure of APB included many zero values and a non-normal distribution of the non-zero measurements, Tobit linear regression (using PROC LIFEREG) was performed for log (APB + 1).[26] For all statistical testing, two-sided p values were reported and a p value < 0.05 was considered statistically significant.

Results

The study cohort comprised 3222 subjects with sESAM measurement of whom 2398 underwent measurement of CAC, 2200 AWT, 2210 APB, and 2314 AC. The median age of the study population was 44 years [IQR 37–52]; 56% were women, 50% African-American. This study population is statistically similar to the 3557 subjects in the entire DHS sample that had blood obtained during Visit 2 (data not shown).[20]

Increasing quartiles of sESAM were associated with all traditional cardiac risk factors except for current smoking and family history of myocardial infarction as well as with multiple inflammatory, renal, and other novel biomarkers (Table 1; Online Data Supplement: Table I; please see http://atvb.ahajournals.org). Levels of sESAM were higher in men vs. women (median 35.2 [27.5–44.5] vs. 34.0 [26.8–42.3] ng/mL; p=0.006) and higher in Caucasian vs. African-American subjects (median 35.7 [29.5–43.5] vs. 33.7 [26.0–43.1] ng/mL, p < 0.0001). Levels of sICAM-1 and sVCAM-1 also associated with most cardiovascular risk factors but did not differ by sex or race (Online Data Supplement: Tables III and IV; please see http://atvb.ahajournals.org). In analyses stratified by race, no differences in sICAM-1 were observed between individuals with and without the rs5491 SNP in the ICAM-1 gene (Online Data Supplement: Table V; please see http://atvb.ahajournals.org).

sESAM was only weakly correlated with both sICAM-1 and sVCAM-1 (sICAM-1: Spearman ρ=0.18, p<0.0001; sVCAM-1: ρ=0.26, p<0.0001). Conversely, sICAM-1 and sVCAM-1 were highly correlated (ρ=0.60, p<0.0001). The strongest correlations between sESAM and the continuous variables tested included cystatin C (ρ=0.40; p<0.0001), MCP-1 (ρ=0.31; p<0.001), eGFR (ρ=−0.23; p<0.001), and interleukin-18 (ρ=0.21; p<0.0001) (Table 2). Blood pressure,

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lipids, measures of obesity and insulin resistance, and other selected inflammatory biomarkers were weakly correlated with sESAM ($\rho<0.2$, $p<0.0001$ for each; Online Data Supplement: Table II; please see http://atvb.ahajournals.org).

CAC prevalence, aortic plaque prevalence (AP), and AWT increased significantly and AC decreased significantly across sESAM quartiles (Table 1; Figure 1). Similar univariable associations with CAC, AWT, AP, APB, and AC were observed when sESAM was analyzed as a continuous variable (Table 3).

CAC prevalence increased modestly across quartiles of sICAM-1 ($p_{trend} = 0.047$) and sVCAM ($p_{trend} = 0.064$) (Figure 1), but no association was observed with aortic plaque (Online data supplement: Tables III and IV; please see http://atvb.ahajournals.org). When sICAM-1 and sVCAM-1 were analyzed as log-transformed continuous variables, no significant associations were observed with prevalent CAC, AP, or APB (Table 3). However, both sICAM-1 and sVCAM-1 significantly associated with AWT and AC in unadjusted analyses ($p\leq0.001$ for each; Table 3).

In multivariable models adjusting for traditional risk factors, the associations between sESAM and atherosclerosis phenotypes remained significant for CAC (adjusted OR 1.2 per SD increase, 95% CI 1.1–1.3; p=0.005), AWT (p=0.035), and AC (p=0.006) but were attenuated for AP and APB (AP: p=0.34; APB: p=0.15) (Table 3: Model 1). Adjustment for sICAM-1 and sVCAM-1 (Table 3: Model 2) as well as for MCP-1 and hsCRP (Table 3: Model 3) had no significant effect on the point estimates for sESAM. After adjustment for traditional risk factors and other biomarkers, sICAM-1 and sVCAM-1 were not associated with any atherosclerosis phenotype (Table 3). Exclusion of subjects with a self-reported history of myocardial infarction (n=68) did not significantly alter any of the associations. Because endothelial dysfunction is correlated with atherosclerosis, analyses for AC were restricted to subjects with CAC score < 10 (n=1938) and did not significantly alter any of the associations (data not shown).

Because sICAM-1 and sVCAM-1 required log transformation for all linear models, parallel analyses were repeated replacing sESAM with log sESAM, and no differences in the results of the analyses reported in Table 3 were noted. Additionally, use of untransformed sICAM-1 and sVCAM-1 weakened the unadjusted associations between these soluble CAMs and all of the atherosclerosis phenotypes.

Discussion

In this first reported study of plasma levels of sESAM in humans, we observed significant associations of this novel cellular adhesion molecule (CAM) with traditional cardiac risk factors, renal function, and multiple inflammatory and non-inflammatory biomarkers implicated in CHD. sESAM was modestly but significantly associated with coronary calcium and abdominal aortic wall thickness, measures of subclinical atherosclerosis at different stages of lesion development in different vascular beds, even when adjusted for traditional risk factors as well as other soluble CAMs including sICAM-1 and sVCAM-1. Additionally, sESAM was independently associated with decreased aortic compliance, a functional measure of vascular stiffness. Given the weak correlation of sESAM with both sICAM-1 and sVCAM-1 and the lack of independent association of sICAM-1 and sVCAM-1 with any atherosclerosis phenotype within the same study sample, our findings support a distinct role for sESAM in atherosclerosis apart from other adhesion molecules.

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Soluble Adhesion Molecules and Atherosclerosis

Prior studies on sICAM-1 and sVCAM-1 have reported mixed associations with atherosclerosis as well as cardiovascular events.[10] In case-control and cohort studies of healthy subjects similar to the design of the DHS, sICAM-1 has typically demonstrated modest independent associations with carotid intima media thickness, carotid and femoral artery plaques, aortic valve calcium, and incident cardiovascular events (Online Data Supplement, Table VI; please see http://atvb.ahajournals.org).[27–34] Conversely, most rigorous studies with sVCAM-1 have reported no significant associations with similar endpoints,[29–31, 34, 35] consistent with our null findings (Online Data Supplement, Table VI; please see http://atvb.ahajournals.org). In the few reported studies of plasma levels of soluble CAMs and CAC, sICAM-1 was not independently associated with prevalent CAC, a finding similar to ours.[36–38]

sESAM, Diapedesis and Atherosclerosis

ESAM was cloned in 2001 and found to be a transmembrane type I glycoprotein member of the immunoglobulin superfamily.[6] Unlike other CAMs which are expressed in multiple cell types, ESAM is a JAM-related molecule solely expressed in endothelial tight junctions and activated platelets.[6, 7] ESAM selectively regulates transmigration of neutrophils and monocytes but not lymphocytes across human endothelial cells and does not affect the number of adherent or rolling cells.[8, 9] In murine models of atherosclerosis, ESAM gene deletion is associated with markedly reduced aortic atherosclerotic lesion size and reduced monocyte adhesion and endothelial transmigration.[9] These observations, along with the findings of a significant association between plasma levels of sESAM and subclinical atherosclerosis in our study, suggest that ESAM may represent an intriguing target for studying the role of leukocyte diapedesis in atherosclerosis.

sESAM and Atherosclerosis Measures

sESAM was modestly but independently associated with measures of both coronary (CAC) and peripheral atherosclerosis (AWT). CAC is a validated non-invasive measure of late-stage pre-clinical atherosclerosis and is associated with CHD events.[39] Abdominal AWT as measured by abdominal MRI is a novel measure of peripheral atherosclerosis that is conceptually similar to carotid intima media thickness and is associated with traditional cardiac risk factors in our population sample (data not shown). Aortic wall thickening likely represents an earlier stage of atherosclerosis than coronary calcification, but future studies are needed to validate its association with CHD. Although sESAM associated with abdominal aortic plaque in univariable analyses, adjustment for traditional risk factors attenuated these associations.

sESAM and Vascular Stiffness

Increasing sESAM levels were inversely associated with aortic compliance, a measure of vascular stiffness. Decreased aortic compliance precedes the development of atherosclerosis,[40, 41] and is inversely associated with atherosclerotic burden when plaques are present.[42] Human studies have shown that decreased aortic compliance is associated with increased risk of premature CHD[43] and increased cardiovascular events over long-term follow-up.[44] Aortic compliance correlates with endothelial function and is decreased in those with endothelial dysfunction, even without clinically evident atherosclerosis.[45]

Study Limitations and Strengths

There are several limitations to our study. First, the cross-sectional study design and lack of clinical endpoints limits the clinical implications of the study. There are multiple molecules involved in leukocyte transmigration,[46] and sESAM may be a marker of another causal pathway relating diapedesis to atherosclerosis. Importantly, we measured soluble ESAM and did not assess cell surface expression. At present, it is not clear that soluble levels of CAMs

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provide an accurate reflection of cellular expression: shedding of cell surface receptors into the circulation may vary depending on the clinical condition.[10, 47]

These limitations are balanced by several strengths: our large population-based sample and consistency of findings across different statistical models and different vascular beds strengthen the validity of our results. The measurement of multiple soluble adhesion molecules and atherosclerosis phenotypes within the same study sample allow for a comprehensive comparison of the relative associations of different CAMs with atherosclerosis. Our measurement of sICAM-1 in over 1,000 African-Americans was not affected by the rs5491 SNP;[24, 48] therefore, we were able to assess the impact of race on levels of soluble CAMs and atherosclerosis.

Conclusions

sESAM is independently associated with measures of both prevalent coronary (coronary calcium) and peripheral (abdominal aortic wall thickness) atherosclerosis as well as with increased vascular stiffness (aortic compliance). sICAM-1 and sVCAM-1 were highly correlated with each other but not with sESAM and were not independently associated with any atherosclerosis phenotype, suggesting a distinct biological role for sESAM in atherosclerotic plaque development.

Condensed abstract

We hypothesized that soluble endothelial-cell selective adhesion molecule (sESAM) is associated with atherosclerosis and vascular stiffness in the Dallas Heart Study, a cross-sectional population-based sample. In multivariate analyses, sESAM was independently associated with prevalent coronary calcium, abdominal aortic wall thickness, and aortic compliance. In contrast, no independent associations were observed between sICAM-1 or sVCAM-1 and any of the atherosclerosis phenotypes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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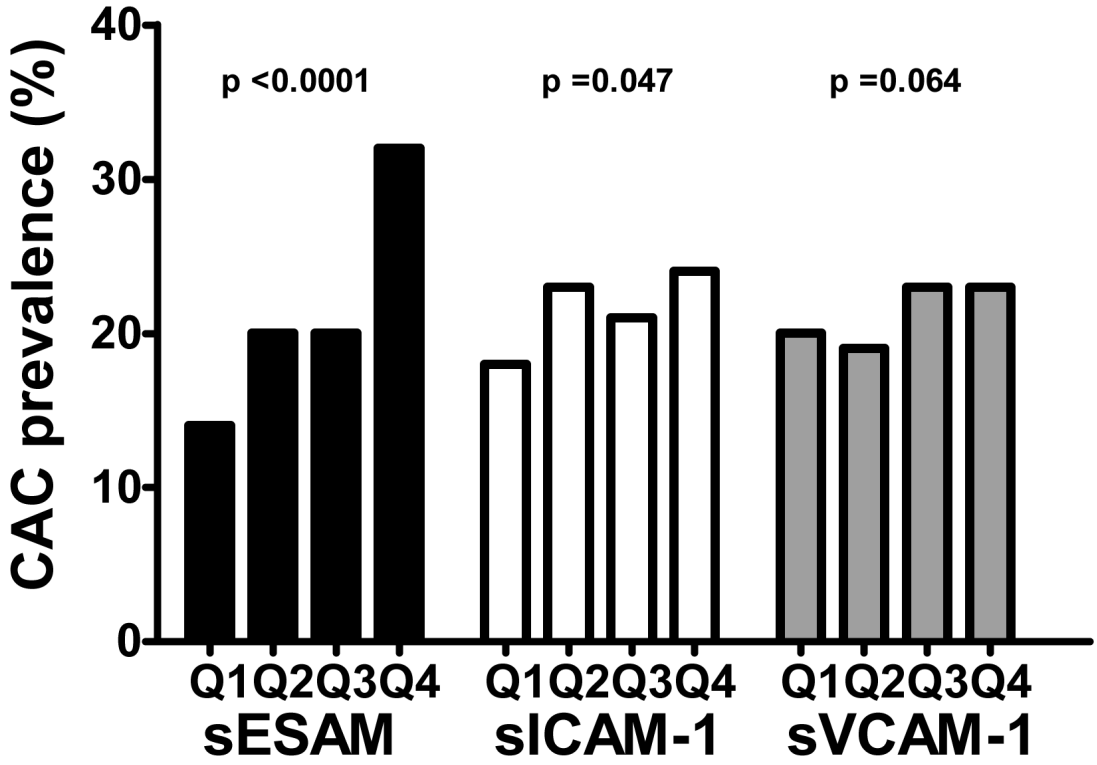

Figure 1. Prevalence of Coronary Calcium (CAC) Across Quartiles of Soluble Cellular Adhesion Molecules

Percentage of subjects with Coronary Calcium (CAC) score>10 across sex- and race-specific quartiles of sESAM, sICAM-1, and sVCAM-1.

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Table 1

Demographic and clinical variables across quartiles of sESAM (N=3222)

Variable	Q1	Q2	Q3	Q4	p-trend
sESAM, ng/mL	2.1–27.1	27.1–34.4	34.4–43.2	43.2–145.0	
Age, years	40 [34, 48]	43 [36, 51]	44 [37, 52]	48 [39, 56]	<0.0001
Male sex	42%	43%	44%	48%	0.011
African-American	60%	49%	46%	51%	<0.0001
Caucasian	22%	31%	35%	31%	<0.0001
Hispanic	17%	17%	17%	17%	0.9
Hypertension	27%	30%	33%	47%	<0.0001
Diabetes	7%	9%	12%	19%	<0.0001
Metabolic Syndrome	26%	29%	35%	44%	<0.0001
Current Smokers	28%	27%	29%	32%	0.06
Low HDL	35%	40%	45%	46%	<0.0001
Hypercholesterolemia	8%	12%	14%	18%	<0.0001
Hypertriglyceridemia	9%	11%	12%	17%	<0.0001
Family history of MI	10%	11%	10%	12%	0.3
Body Mass Index	29.1 [25.2, 33.5]	29.1 [25.3, 34.6]	29.3 [25.4, 34.3]	30.3 [25.7, 35.7]	0.001
hsCRP, mg/L	2.3 [0.9, 5.2]	2.4 [1.0, 6.2]	2.9 [1.3, 7.2]	4.2 [1.8, 10.2]	<.0001
MCP-1,pg/ml	142 [105, 191]	161 [122, 210]	175 [130, 227]	211 [152, 284]	<.0001
sICAM-1, ng/mL	546 [409, 759]	585 [417, 767]	611 [464, 831]	707 [515, 966]	<.0001
sVCAM-1, ng/mL	847 [651, 1135]	930 [691, 1267]	1032 [766, 1444]	1203 [861, 1743	<.0001
Aortic wall thickness (AWT), mm	1.61 [1.46, 1.77]	1.64 [1.46, 1.8]	1.66 [1.47, 1.83]	1.72 [1.54, 1.93]	<.0001
Aortic compliance (AC), ml/mmHg	26.2 [19.1, 34.6]	24.0 [16.5, 32.4]	23.5 [16.5, 31.1]	20.2 [13.7, 28.9]	<0.0001
Coronary calcium (CAC) > 10 units	14%	20%	20%	32%	<.0001
Detectable Aortic Plaque (AP)	33%	36%	38%	47%	<.0001

Values are medians [interquartile range] for continuous variables and percentages for categorical variables.

BMI= body mass index; eGFR=estimated glomerular filtration rate; HOMA-IR= homeostasis model assessment index; hsCRP=high sensitivity C-reactive protein, MCP-1= monocyte chemoattractant protein-1; sCD40L=soluble CD40 ligand.

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Table 2

Spearman Correlation Coefficients Between sESAM, sICAM-1, and sVCAM-1 and Continuous Variables

Variable	sESAM	p-value	sICAM-1	p-value	sVCAM-1	p-value
Cystatin C	0.40	<.0001	0.109	<.0001	0.055	0.002
MCP-1	0.31	<.0001	0.188	<.0001	0.234	<.0001
eGFR	−0.23	<.0001	−0.01	0.474	−0.02	0.182
IL-18	0.21	<.0001	0.14	<.0001	0.10	<.0001
Age	0.20	<.0001	0.07	0.000	0.08	<.0001
Triglycerides	0.20	<.0001	0.13	<.0001	0.15	<.0001
sCD40L	0.18	<.0001	0.07	0.000	0.14	<.0001
hsCRP	0.18	<.0001	0.08	<.0001	0.08	<.0001

Values are Spearman rank correlation coefficients (rho) listed in order of magnitude for sESAM. eGFR= estimated glomerular filtration rate; hsCRP= high sensitivity C-reactive protein, MCP-1= monocyte chemoattractant protein-1; sCD40L= soluble CD40 ligand.

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Table 3

Association of sESAM, sICAM-1, and sVCAM-1 with Atherosclerosis Phenotypes

	Models	sESAM OR [95%CI]†	p value	Log sICAM-1 OR [95%CI]†	p value	Log sVCAM-1 OR [95%CI]†	p value
CAC N=2398	**Unadjusted**	1.5 [1.3–1.6]	<0.0001	1.1 [1.0–1.2	0.055	1.1 [0.99–1.2]	0.09
	Model 1*	1.2 [1.1–1.3]	0.005	1.0 [0.9–1.1]	0.98	1.0 [0.9–1.1]	0.99
	Model 2*	1.2 [1.1–1.3]	0.005	0.98 [0.8–1.1]	0.79	0.98 [0.8–1.1]	0.77
	Model 3*	1.2 [1.1–1.3]	0.004	1.0 [0.9–1.2]	0.97	1.0 [0.8–1.1]	0.70
AP N=2187	**Unadjusted**	1.2 [1.1–1.3]	<0.0001	1.1 [1.0–1.2]	0.056	1.1 [0.99–1.2]	0.07
	Model 1*	1.1 [0.95–1.2]	0.34	1.0 [0.9–1.1]	0.95	1.0 [0.9–1.1]	0.77
	Model 2*	1.1 [0.96–1.2]	0.29	0.98 [0.9–1.1]	0.73	1.0 [0.9–1.2]	0.72
	Model 3*	1.1 [0.95–1.2]	0.29	1.0 [0.9–1.1]	0.98	1.0 [0.89–1.2]	0.83
		Beta‡	**p value**	**Beta‡**	**p value**	**Beta‡**	**p value**
AWT N=2200	**Unadjusted**	0.050	<0.001	0.02	0.000	0.02	0.001
	Model 1*	0.012	0.035	0.006	0.31	0.005	0.37
	Model 2*	0.013	0.039	0.005	0.56	0.000	0.99
	Model 3*	0.015	0.018	0.007	0.40	−0.001	0.92
APB N=2210	**Unadjusted**	0.225	<0.0001	0.087	0.04	0.075	0.08
	Model 1*	0.041	0.25	−0.019	0.60	−0.001	0.99
	Model 2*	0.049	0.18	−0.032	0.50	0.014	0.77
	Model 3*	0.046	0.21	−0.030	0.53	0.0016	0.75
AC n=2314	**Unadjusted**	−1.87	<0.0001	−0.85	0.0004	−0.95	<0.0001
	Model 1*	−0.55	0.006	−0.34	0.08	−0.42	0.03
	Model 2*	−0.50	0.015	−0.02	0.93	−0.30	0.26
	Model 3*	−0.49	0.02	0.001	0.99	−0.29	0.28

CAC=coronary artery calcium prevalence; AWT= abdominal aortic wall thickness; AP=abdominal aortic plaque prevalence; APB=abdominal aortic plaque burden; AC=aortic compliance

*Model 1: adjusted for age, sex, race, hypertension, diabetes, current smoking, hypercholesterolemia, hypertriglyceridemia, low HDL-C, and BMI; Model 2: Model 1 plus sESAM, log sICAM-1 and log sVCAM-1; Model 3: Model 2 plus MCP-1 and hsCRP

†Odds ratios reflect a 1 SD increase (sESAM; 16.5 ng/mL; log sICAM-1: 0.50; log sVCAM-1: 0.52)

‡Beta estimates for AWT and AC derived from linear regression and for APB derived from Tobit linear regression per 1 SD increase in ESAM, log sICAM-1, and log sVCAM-1