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Research Article

Elevated Soluble Vascular Cell Adhesion Molecule-1 Is Associated With Cerebrovascular Resistance and Cognitive Function

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Abstract

Background: Elevated plasma soluble vascular cell adhesion molecule-1 (sVCAM-1) is a presumed marker of endothelial dysfunction, both in the brain and systemic circulation. Impairments in memory and cognition have been associated with cardiovascular diseases, but little is known about their relationships to abnormal cerebral endothelial function.

Methods: We studied the cross-sectional association between sVCAM-1 and markers of cerebrovascular hemodynamics and cognitive function in 680 community-dwelling participants in the MOBILIZE Boston Study, aged 65 years and older. Cognitive function was assessed using the Hopkins Verbal Learning Memory Test and Trail Making Tests (TMTs) A and B. Global cognitive impairment was defined as Mini-Mental State Examination (MMSE) score less than 24. sVCAM-1 was measured by ELISA assay. Beat-to-beat blood flow velocity (BFV) and cerebrovascular resistance (CVR = mean arterial pressure / BFV) in the middle cerebral artery were assessed at rest by transcranial Doppler ultrasound.

Results: sVCAM-1 concentrations were higher among participants with an MMSE score <24 versus ≥24 (1,201 ± 417 vs 1,122 ± 494 ng/mL). In regression models adjusted for sociodemographic characteristics and health conditions, increasing levels of sVCAM-1 were linearly associated with higher resting CVR ($p = .006$) and lower performance on the Hopkins Verbal Learning Memory (immediate recall and delayed recall) and adjusted TMT B tests ($p < .05$). Higher levels of sVCAM-1 were also associated with global cognitive impairment on the MMSE (odds ratio = 3.9; 95% confidence interval: 1.4–10.9; $p = .011$).

Conclusions: In this cohort of elderly participants, we observed a cross-sectional association between elevated sVCAM-1 levels and both cognitive impairment and increased cerebrovascular resistance. Longitudinal studies are needed to determine whether elevated sVCAM-1 is a cause or consequence of cerebrovascular damage.

Keywords: Cerebrovascular resistance—Cognitive impairment—Endothelium—Executive function—sVCAM-1

Cognitive impairments and vascular diseases are increasingly prevalent worldwide in older adults, conferring a major burden on health and health care costs (1,2). Many studies suggest that these conditions may be linked through the development of cerebral endothelial dysfunction and associated cerebral microvascular disease. Previous studies suggest that hypertension may impair cerebrovascular reactivity (3). Hypertension has also been implicated in vascular cognitive impairment (4,5) and Alzheimer's disease (6,7), and both of these conditions have a significant vascular pathology. Cerebral endothelial dysfunction may be due to a number of conditions associated

with aging, including hypertension and type 2 diabetes (8,9). It may also impair cerebral blood flow regulation and cerebral vasoreactivity, and ultimately lead to mobility impairments, including slowing of gait and falls (10,11).

Soluble vascular cell adhesion molecule-1 (sVCAM-1) is a well-known biomarker of endothelial dysfunction that is associated with hypertension and atherosclerosis (12,13). It plays an important role in accelerating atherosclerosis by facilitating the attachment of inflammatory cells to the vascular endothelial wall and promoting their subsequent migration through the endothelium (1,14). The resulting inflammatory response, injury, and stiffening of the vascular wall may result in impaired cerebral blood flow regulation, especially endothelium-dependent vasodilatation in response to changes in blood pCO_2, and ischemic damage to the cerebral microvasculature.

We have shown in a previous study that elevated plasma levels of sVCAM-1 may be a marker of chronic cerebral blood flow dysregulation due to cerebral endothelial damage from hypertension and may also signal the clinical consequences of cerebral microvascular disease, including slow gait speed and injurious falls among elderly people (10).

We hypothesized that an elevated plasma concentration of sVCAM-1 may be a marker of cerebral microvascular disease, characterized by increased cerebrovascular resistance and lower cognitive performance in elderly people. We therefore used transcranial Doppler ultrasonography, plasma biomarkers, and cognitive data from the MOBILIZE Boston Study to explore the relationships between plasma levels of sVCAM-1, cerebrovascular resistance, executive dysfunction, and cognitive impairment in a community-based population of older adults.

Materials and Methods

Participants

The study sample consisted of 680 community-dwelling older adults living in the Boston area who participated in the MOBILIZE Boston Study. The design and methodology for this study have been previously described in detail (15,16). To be included, individuals had to be 70 years or older (or age > 65 years if living with a participant), able to understand and communicate in English, and able to walk 20 feet without personal assistance. Exclusion criteria included terminal disease, severe vision or hearing deficits, and a Mini-Mental State Examination (MMSE) score less than 18 (15,16). All participants underwent a complete home and laboratory assessment of demographic characteristics, medical history, medications, functional status, gait speed, smoking status, alcohol use, blood pressure (BP), and cerebral hemodynamics at baseline. Only a subset of 419 participants had an adequate temporal acoustic window to obtain reliable Doppler measures of cerebral blood flow velocity (BFV) and were able to complete the cerebral hemodynamic assessments. Only those participants with complete data for the variables of interest were included in the analyses.

Neuropsychological Measures

We administered neuropsychological tests to each participant during the home interview, as previously described (17,18). The primary outcome was cognitive impairment assessed according to the MMSE score (19,20). Study participants were categorized into two groups according to baseline MMSE score: those with or without significant global cognitive impairment (MMSE score < 24 and ≥ 24, respectively).

The *Hopkins Verbal Learning Test-Revised* (HVLT-R) (21) is a 12-item word list learning test in which individuals are presented three learning and recall trials followed by a delayed recall trail and a 24-item word recognition test. The HVLT-R produces three scores: the sum of correct responses in each of three learning trials (HVLT-R learning), the number of items correctly recalled after the delay (HVLT-R delayed recall), and the number of recognition items correctly identified (HVLT-R recognition). In older adults, the encoding procedure relies on working and verbal memory processes and executive function (22).

The *Trail Making Test* (TMT) Part A consists of number targets to be connected in order, providing an estimate of attention and psychomotor speed. TMT Part B includes number and letter targets that are to be connected in alternating sequence, providing an estimate of set shifting and executive function (23). As in previous studies (17,18), to control for the effect of motor function and information processing speed, we calculated the "adjusted" TMT as the time to perform part B minus the time to perform part A.

Activity of Daily Living score (ADL): The index of ADLs counts the number of ADLs for which a person needs help and is the classic measure of the severity of the need for personal assistance services and other long-term services and supports (24). *Instrumental Activity of Daily Living score (IADL):* This index measures a participant's ability to maintain independence in household chores, cooking, shopping, finances, and transportation (25).

Biomarker Measures

Concentrations of soluble intercellular adhesion molecule-1 (sICAM-1), sVCAM-1, and interleukin-6 (IL-6) were measured by ELISA assay (R&D Systems, Minneapolis, MN). For sICAM-1, this assay has a sensitivity of 0.35 ng/mL and the day-to-day variability of the assay at concentrations of 64.2, 117, 290, and 453 ng/mL are 10.1, 7.4, 6.0, and 6.1%, respectively. For sVCAM-1, the assay has a sensitivity of 2.0 ng/mL and the day-to-day variability of the assay at concentrations of 9.8, 24.9, and 49.6 ng/mL are 10.2, 8.5, and 8.9%, respectively. For IL-6, the assay has a sensitivity of 0.094 pg/mL and the day-to-day variability of the assay at concentrations of 0.49, 2.78, and 5.65 pg/mL are 9.6, 7.2, and 6.5%, respectively. The concentration of high-sensitivity C-reactive protein was determined using an immunoturbidimetric assay on the Hitachi 917 analyzer (Roche Diagnostics, Indianapolis, IN), using reagents and calibrators from DiaSorin (Stillwater, MN). This high-sensitivity assay has a limit of detection of 0.03 mg/L. The day-to-day variability of the assay at concentrations of 0.91, 3.07, and 13.38 mg/L are 2.81, 1.61, and 1.1%, respectively. All assays were performed by Dr. Nader Rifai's group at Boston Children's Hospital. The biomarker measurement methodology has been previously described in detail (10).

Transcranial Doppler Ultrasound Measures

Participants reported to the Cerebrovascular Laboratory at the Hebrew SeniorLife Institute for Aging Research and were instrumented for heart rate (ECG) and beat-to-beat arterial pressure monitoring (ABP, Finapres, Ohmeda Monitoring Systems, Englewood, CO). Transcranial Doppler (TCD) ultrasonography (MultiDop X4, DWL-Transcranial Doppler Systems, Sterling, VA) was used to measure middle cerebral artery mean BFV at rest (26). The middle cerebral artery signal was identified according to standard criteria and recorded at a depth of 50–60 mm (26). Resting BFV was quantified as the average BFV over each beat of the heart during the last minute of a 5-minute period while participants sat quietly in a chair.

Cerebrovascular resistance (CVR) was calculated for each beat during this period as the mean arterial BP divided by the BFV, then averaged. CVR represents the resistance of downstream arterioles beyond the middle cerebral artery, which normally constrict or dilate to help regulate blood flow. A higher CVR reduces blood flow to regions of the brain.

Other Covariates

Covariates included sociodemographic characteristics, cardiovascular risk factors, health status, and amount of physical activity. Sociodemographic characteristics included age, sex, race (self-identified), and years of education. We used the validated Physical Activity Scale for the Elderly (PASE) to measure physical activity in the previous week (27). Participants were asked about physician-diagnosed major medical conditions. Diabetes was defined using an algorithm based on self-reported diabetes, use of antidiabetic medications, and laboratory measures, including random glucose (≥200 mg/dL) and hemoglobin A_{1c} (≥7%). Body mass index (calculated as weight in kilograms divided by height in meters squared) was calculated from measured height and weight. Comorbidity index was the number of comorbidities or medical conditions. Certain medication use (antihypertensives, antidepressants, and benzodiazepines) was also assessed. Hypertension was defined using three BP categories: Normotension, no history or current evidence of hypertension; controlled hypertension, a history of hypertension and antihypertensive treatment with normal BP (systolic BP < 140 and diastolic BP < 90 during the baseline clinical assessment); and uncontrolled hypertension, a history of hypertension with abnormal BP (systolic BP ≥ 140 or diastolic BP ≥ 90) (28,29).

Smoking and alcohol

Smoking status was determined by asking whether the participant currently smoked cigarettes. Alcohol use was assessed with a question on whether individuals consumed two or more drinks of beer, wine, or liquor each week.

Ethics Statement

The MOBILIZE Boston Study was reviewed and approved by the Hebrew SeniorLife Institutional Review Board. Written informed consent was obtained from each participant. The study was conducted according to the principles of the Helsinki Declaration.

Data Analysis

We compared baseline characteristics of different groups of study participants by using *t* tests, χ^2 tests, or Wilcoxon rank-sum tests. We used multivariate linear regression to examine the cross-sectional relationships between log-transformed sVCAM-1 levels and continuous outcomes (eg, CVR, TMTs A and B) and logistic regression to estimate the relative risk and 95% confidence intervals for quintiles of sVCAM and binary outcomes (eg, cognitive impairment [MMSE score < 24]).

Analyses were adjusted for the following groups of potential confounders: (i) other biomarkers (ICAM-1, IL-6, and C-reactive protein), (ii) sociodemographic conditions (age, gender, White race, education level, body mass index, current smoker, and alcohol use), (iii) health conditions (diabetes, hypertension, heart failure, hyperlipidemia, depression, any cardiovascular medications, coronary artery disease, and previous stroke), and (iv) physical activity level.

Participants with missing data for the main outcomes, sVCAM-1, cognition status, neuropsychological measures, or CVR were excluded from those specific analyses. No imputing methods were used. All analyses were performed using SAS software, version 9.3 (SAS Institute, Cary, NC). A two-sided *p* value of less than .05 was considered indicative of statistical significance.

Results

Participants

Table 1 shows the characteristics of participants with and without cognitive impairment. The mean age of participants was 78.1 ± 5.4 years and 62.4% were women. Of the study participants, 361 (53.7%) had controlled hypertension and 162 (24.1%) had uncontrolled hypertension. TCD measures were available for 419 (62%) participants. There was no significant difference in demographics or the number of participants with cognitive impairment between those with and without TCD data.

Soluble VCAM-1, BFV, and Cerebrovascular Resistance

In a cross-sectional analysis, elevated sVCAM-1 levels were associated with higher resting CVR ($p = .04$; Figure 1). After adjustment for relevant covariates, increasing levels of sVCAM-1 were linearly associated with higher resting CVR ($p = .006$; Supplementary Table 1). An increase in resting CVR was also correlated with a reduction in cognitive performance ($r = .13$, $p = .015$).

Soluble VCAM-1 and Neuropsychological Measures

Soluble VCAM-1 and global cognitive impairment (MMSE ≤ 24)

sVCAM-1 concentration was higher among participants with an MMSE score <24 versus ≥24 (1,201 ± 417 vs 1,122 ± 494 ng/mL; $p = .029$; Table 1**).** This association persisted in multivariate logistic regression analyses, which showed that higher levels of sVCAM-1 were associated with cognitive impairment (odds ratio = 3.9; 95% confidence interval: 1.4–10.9; $p = .01$; Table 2**).** After adjustment for relevant covariates, higher levels of sVCAM-1 were cross-sectionally associated with lower MMSE scores (−0.14; −0.18 to −0.09; $p = .003$; Supplementary Table 2**).**

Soluble VCAM-1 and HVLT

The mean scores of HVLT subtests were 20.8 ± 5.8 for the immediate recall component and 6.3 ± 3.5 for the delayed recall component. In multivariate analysis, higher levels of sVCAM-1 were associated with higher risk of having poorer performance on the HVLT test ($p < .05$; Table 3).

Soluble VCAM-1 and Adjusted TMT B

The mean scores of TMT were Part A = 56.3 ± 34.2; Part B = 141.1 ± 78.1 and the difference = 87.9 ± 63.7. In multivariate analysis, sVCAM-1 levels were linearly associated with adjusted TMT B test scores ($p = .014$; Table 3).

Soluble VCAM-1, ADL, and IADL

Of the study participants, 148 (22.2%) had little or lot of difficulty in performing ADLs (ADL ≥ 1) and 287 (42.9%) reported having difficulty in an IADL (IADL ≥ 1). In univariate analysis, elevated levels of sVCAM-1 were linearly associated with lower ADL ($p < .0001$) and IADL scores ($p < .0001$). After adjustment for relevant covariates, the association was still statistically significant ($p < .0001$; Table 3).

Table 1. Characteristics of Participants According to Cognitive Status (MMSE < 24 vs ≥ 24), *N* = 668

Baseline Characteristics	Total Sample	Cognitive Status*		*P* value
		Impairment (*n* = 72, 11%)	No Impairment (*n* = 596, 89%)	
Demographics				
Age, mean (±*SD*), y	78.1 ± 5.4	78.7 ± 5.9	78.0 ± 5.3	.19
Women	418 (62.6)	51 (70.8)	367 (61.6)	.07
White race	535 (80.1)	32 (44.4)	503 (84.4)	<.0001
Educational level, mean (±*SD*), y	14.8 ± 6.1	13.1 ± 11.9	15.2 ± 4.8	<.0001
Health behaviors				
Body mass index, kg/m² †				
<25	210 (31.4)	15(20.8)	195 (32.7)	
25–29.9	286 (42.8)	32 (44.4)	254 (42.6)	.06
≥30	172 (25.7)	25 (34.7)	147 (24.7)	
Current smoker	391 (58.5)	24 (33.33)	361 (60.6)	<.0001
Alcohol use (≥2 drinks per week)	174 (26.0)	6 (8.33)	165 (27.68)	.0004
Physical activity score‡				
0–66	209 (31.3)	26 (36.11)	183 (30.70)	
66.01–124	226 (33.8)	30 (41.7)	196 (32.89)	.069
124.01–559	233 (34.9)	16 (19.5)	217 (36.4)	
Health conditions				
Comorbidity index, mean (±*SD*)	3.0 ± 1.6	3.2 ± 1.6	3.0 ± 1.6	.9
Hypertension	529 (79.2)	71 (98.6)	458 (76.9)	.0001
Hyperlipidemia	391 (58.5)	48 (66.7)	343 (57.6)	.37
Diabetes	126 (18.9)	22 (30.6)	104 (17.5)	.007
Previous stroke	71 (10.6)	7 (9.7)	64 (10.7)	.9
Coronary artery disease	117 (17.5)	17 (23.6)	100 (16.8)	.3
Congestive heart failure	43 (6.4)	7 (9.7)	36 (6.0)	.7
CESD-R score mean (±*SD*)	11.3 ± 11.2	15.3 ± 15.3	10.4 ± 10.4	.02
Medications				
Any cardiovascular medication	460 (68.9)	61(84.7)	399 (67.0)	.002
Psychotropic medication	53 (7.9)	10 (13.9)	43 (7.2)	.04
Neuropsychological measures				
TMT A Score, mean (±*SD*), s	56.3 ± 34.2	71.4 ± 38.1	59.3 ± 32.2	.041
TMT B Score, mean (±*SD*), s	141.1 ± 78.1	168.1 ± 88.3	121.1 ± 79.0	.016
HVLT, immediate recall, mean (±*SD*)	20.8 ± 5.8	29.6 ± 7.5	16.8 ± 5.1	.04
HVLT, delayed recall, mean (±*SD*)	6.3 ± 3.5	10.1 ± 4.1	4.3 ± 3.6	.03
HVLT, recognition, mean (±*SD*)	11.4 ± 2.2	14.7 ± 3.2	8.1 ± 2.3	.012
Functional measures				
IADL score ≥ 1	287 (42.9%)	69 (95.8%)	218 (36.6%)	.0001
ADL score ≥ 1	148 (22.2%)	58 (80.5%)	90 (15.1%)	.0001
Neurophysiologic measures§				
Cerebral BFV, mean (*SD*)	41.0 ± 10.3	37.6 ± 10.1	41.2 ± 10.3	.03
Cerebrovascular resistance, mean (*SD*)	1.8 ± 0.6	2.0 ± 0.6	1.7 ± 0.6	.04
Biomarkers measures				
C-reactive protein, mean (±*SD*), mg/L	4.2 ± 13	6.4 ± 12	3.9 ± 13	.002
Interleukin-6, mean (±*SD*), pg/mL	4.0 ± 7.3	3.9 ± 7.3	3.9 ± 3.8	.2
Soluble ICAM-1, mean (±*SD*), ng/mL	262 ± 81	263.0 ± 77	254.3 ± 108	.05
Soluble VCAM-1, mean (±*SD*), ng/mL	1192 ± 428	1201.3 ± 417	1122.8 ± 494	.03

Notes: Global test: χ^2 or Fisher's exact test for binary variables; analysis of variance for continuous variables.

BFV = blood flow velocity; CESD-R = Center for Epidemiological Studies Depression Scale Revised; HVLT = Hopkins Verbal Learning Memory Test; ICAM-1 = intercellular adhesion molecule-1; MMSE = Mini-Mental State Examination; TMT = Trail Making Test.

*Cognitive impairment (MMSE < 24).

†Body mass index is calculated as weight in kilograms divided by height in meters squared.

‡Physical activity tertiles measured using the Physical Activity Scale for the Elderly.

§Transcranial Doppler data in cm/s units for cerebral BFV, mmHg.s/cm units for cerebrovascular resistance.

Soluble ICAM-1 and cognitive function

Mean ICAM-1 levels were 263 ± 78 ng/mL in participants with cognitive impairment and 254 ± 108 ng/mL in participants without impairment ($p = .05$). There were no statistically significant relationships between any of the study outcomes and circulating levels of sICAM-1 in univariate or multivariate analysis.

Discussion

The results of this study show a cross-sectional association between elevated plasma levels of sVCAM-1 and increased cerebrovascular resistance and lower cognitive performance in older adults. To our knowledge, these findings are novel and consistent with the notion that sVCAM-1 is associated with abnormalities in cerebral blood

Table 2. Odds Ratios (95% CIs) for the Cross-sectional Association Between Quintiles of sVCAM-1 and Concurrent Cognitive Impairment Status (MMSE < 24), *N* = 668*

	Quintiles of sVCAM-1, Median (IQR), ng/mL					
	718 (657–809)	935 (900–971)	1,118 (1,071–1,169)	1,333 (1,277–1,390)	1,850 (1,566–2,011)	
N	131	133	136	134	134	*p* for Trend
Model 1†						
Odds ratio (95% CI)	1.00	0.85 (0.39–1.86)	0.61 (0.24–1.59)	0.59 (0.21–1.64)	2.74 (1.14–6.56)	
p Value	Reference	.68	.31	.31	.024	.054
Model 2‡						
Odds ratio (95% CI)	1.00	0.81 (0.37–1.82)	0.63 (0.24–1.95)	0.69 (0.25–1.95)	3.49 (1.39–8.79)	
p Value	Reference	.61	.34	.48	.008	.0049
Model 3§						
Odds ratio (95% CI)	1.00	0.78 (0.34–1.82)	0.56 (0.21–1.56)	0.55 (0.19–1.62)	3.56 (1.22–9.21)	
p Value	Reference	.57	.27	.28	.019	.0040
Model 4‖						
Odds ratio (95% CI)	1.00	0.73 (0.30–1.77)	0.56 (0.20–1.59)	0.66 (0.22–1.97)	3.87 (1.37–10.93)	
p Value	Reference	.49	.27	.45	.011	.0029

Notes: CI = confidence interval; ICAM-1 = intercellular adhesion molecule-1; IQR = interquartile range; sVCAM-1 = soluble vascular cell adhesion molecule-1.
*Missing values = 4 from 672.
†Model 1 = Non adjusted model.
‡Model 2 = Model 1 adjusted for ICAM-1, IL-6, and C-reactive protein.
§Model 3 = Model 2 additionally adjusted for age, gender, White race, education level, body mass index, current smoker, and alcohol use.
‖Model 4 = Model 3 additionally adjusted for hypertension, diabetes, stroke, congestive heart failure, coronary artery disease, hyperlipidemia, depression, psychotropic medication, any cardiovascular medication, and physical activities level.

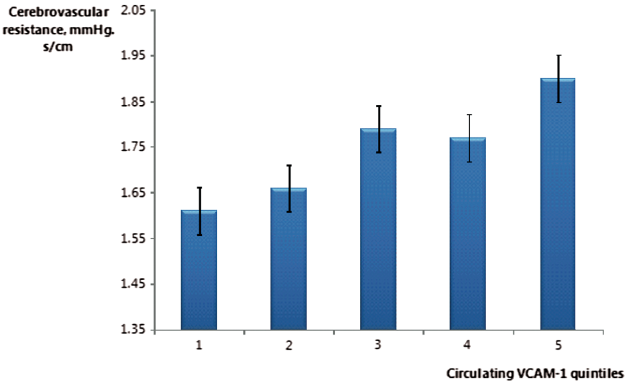

Figure 1. Association between cerebrovascular resistance (mmHg. s/cm) and circulating sVCAM-1 quintiles (*n* = 419).

Table 3. Linear Association Between Cognitive Function Tests and sVCAM-1* (change in score on tests with 10% increase sVCAM-1 in linear regression models), *N* = 668†

Measures	Change in score (95% CI)	*p* Value
Lower scores indicate poorer performance		
MMSE score	−0.14 (−0.2, −0.1)	.003
HVLT immediate recall	−0.2 (−0.3, −0.1)	.04
HVLT delayed recall	−1.6 (−2.3, −0.9)	.03
HVLT recognition	−0.9 (−1.2, −0.6)	.01
Higher scores indicate poorer performance		
TMT A	0.3 (0.2, 0.4)	.043
TMT B	0.5 (0.4, 0.6)	.011
Adjusted TMT B*	0.4 (0.3, 0.5)	.014
IADL score	0.2 (0.1, 0.3)	.002
ADL score	0.2 (0.1, 0.3)	<.001

Notes: ADL = activity of daily living; HVLT = Hopkins Verbal Learning Memory test; IADL = instrumental activity of daily living; MMSE = Mini-Mental State Examination; sVCAM-1 = soluble vascular cell adhesion molecule-1.
*Adjusted TMT B = the time to perform part B minus the time to perform part A.
†Missing values = 4 from 672; all models are adjusted for ICAM-1, IL-6, C-reactive protein, sociodemographic condition and health condition, psychotropic medication, and any cardiovascular medication.

flow regulation and that this may have a clinical or subclinical impact on executive function, cognitive impairment, and functional decline in older people.

VCAM-1 is an endothelial ligand for integrins expressed on leukocytes and platelets, with the function of facilitating endothelial adhesion of circulating leukocytes. The expression of VCAM-1 by endothelial cells is increased in response to inflammatory cytokines (30). The soluble ectodomain of VCAM-1 (sVCAM-1) is proteolytically released from the endothelial cell surface into the circulation upon endothelial activation and injury. Elevated plasma sVCAM-1 levels have been reported in many disease conditions, including coronary and peripheral atherosclerosis, hypertension, and diabetes mellitus (10,31). sVCAM-1 is now a well-established marker for endothelial injury related to inflammatory processes.

The evidence that VCAMs have a role in the progression of atherosclerosis comes from several sources. On histological analysis, human atherosclerotic plaque contains many VCAMs. This may increase peripheral vascular stiffness. It is well known that an increase in peripheral vascular resistance is a hallmark of hypertension. Cellular adhesion molecules increase intimal hyperplasia and the vascular inflammatory response seen after vessel–wall injury (32). Clinical interest in VCAM-1 has grown with the observation that plasma concentrations of VCAM-1 and other inflammatory biomarkers are associated with an increased risk of future vascular events (33).

The results of this study support a vascular mechanism of cognitive impairment. The increase in CVR may be associated with lower blood flow in watershed areas of the brain, resulting in ischemic damage to axons from frontal and prefrontal areas of the brain that control motor function and attentional processes (34,35). Therefore, sVCAM-1 may serve as a physiologic marker, and ultimately a clinical biomarker of cerebral microvascular disease and its clinical consequences such as cognitive and functional decline (36).

Our study had some limitations. First, the cross-sectional design precludes investigating the temporal relation between sVCAM-1 elevation and cerebrovascular resistance, and cognitive impairment. A second limitation is the smaller number of participants with adequate TCD data because of an inadequate temporal bone window to obtain reliable Doppler measures of cerebral BFV. This is a common problem among elderly people, affecting approximately one third of elderly participants in previous studies (37). Therefore, our findings in regard to cerebrovascular hemodynamics may not be generalizable to all older adults. Finally, sVCAM-1 may be related to other processes that impair cognition. By inducing T-cell chemotaxis and inflammatory responses, sVCAM-1 may affect the development of neurodegeneration (38). Inflammatory processes have been linked to the pathogenesis of cognitive impairment (39). We tried to address this by controlling for the inflammatory biomarkers C-reactive protein and IL-6 in the multivariable analysis.

On the other hand, our study has several strengths and potential clinical applications. First, the adhesion molecule (VCAM-1 and ICAM-1) concentrations were comparable with those in previous studies (40). In the future, clinicians may be able to use sVCAM-1 measurements to determine brain endothelial and parenchyma health without the use of expensive imaging studies. This would enable clinicians to intervene early to prevent the clinical consequences of cerebral microvascular disease in elderly people, which include mobility impairments (10), depressive symptoms (41), poor cognitive performance, and functional decline.

Conclusion

In this cohort of community-dwelling elderly participants, we observed a cross-sectional association between soluble VCAM-1 levels and both cognitive function and cerebrovascular resistance. Each of these finding suggests that sVCAM-1 may provide a practical way to detect cerebral endothelial damage and guide future therapeutic interventions. Additional prospective studies are needed to confirm our findings and determine the sequence of events in the pathogenesis of cerebral microvascular disease and its clinical consequences.

Supplementary Material

Please visit the article online at http://gerontologist.oxfordjournals.org/ to view supplementary material.

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Conflict of Interest

G.A.W. has received consulting fees from Environmental Health and Engineering, for work unrelated to this article. The other authors declare no competing financial interests.

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