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Authors

Berardi, Cecilia
Wassel, Christine L
Decker, Paul A
et al.

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Elevated Levels of Adhesion Proteins Are Associated with Low Ankle-Brachial Index: Multi-Ethnic Study of Atherosclerosis

Cecilia Berardi, MD, MS[1,2], **Christine L. Wassel, PhD**[3], **Paul A. Decker, MS**[2], **Nicholas B. Larson, PhD**[2], **Phillip S. Kirsch, MPH**[2], **Mariza de Andrade, PhD**[2], **Michael Y. Tsai, MD, PhD**[4], **James S. Pankow, PhD, MPH**[5], **Michele M. Sale, PhD**[6], **Hugues Sicotte, PhD**[2], **Weihong Tang, MD, PhD**[5], **Naomi Q. Hanson, MS**[4], **Mary M. McDermott, MD**[7], **Michael H. Criqui, MD, MPH**[8], **Michael A. Allison, MD, MPH**[8], and **Suzette J. Bielinski, PhD**[2]

[1]Department of Internal Medicine, Albert Einstein College of Medicine and Montefiore Medical Center, Bronx, NY, USA

[2]Department of Health Sciences Research, Mayo Clinic, Rochester, MN, USA

[3]Department of Pathology and Laboratory Medicine, University of Vermont College of Medicine, Colchester, VT, USA

[4]Laboratory Medicine and Pathology, University of Minnesota, Minneapolis, MN, USA

[5]Division of Epidemiology and Community Health, University of Minnesota, Minneapolis, MN, USA

[6]Center for Public Health Genomics, University of Virginia, Charlottesville, VA, USA

[7]Department of Medicine, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA

[8]Department of Family Medicine and Public Health, University of California, San Diego, La Jolla, CA, USA

Abstract

Inflammation plays a pivotal role in peripheral artery disease (PAD). Cellular adhesion proteins mediate the interaction of leukocytes with endothelial cells during inflammation. To determine the

Corresponding Author: Suzette J. Bielinski, Ph.D., Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA. Tel: +1 507 538 4914; fax: +1 507 284 1516, bielinski.suzette@mayo.edu.
P. S. Kirsch - Present address: UnitedHealthcare, 9700 Health Care Lane, Minnetonka, MN 55343, USA.
E-mail addresses: ceci.berardi@gmail.com (C. Berardi), : cwassel@med.uvm.edu (C. Wassel), Decker.Paul@mayo.edu (P. Decker), Larson.Nicholas@mayo.edu (N. Larson), Phillip_kirsch@uhc.com (P. Kirsch), mandrade@mayo.edu (M. de Andrade), tsaix001@umn.edu (M. Tsai), pankow@umn.edu (J. Pankow), msale@virginia.edu (M. Sale), Sicotte.Hugues@mayo.edu (H. Sicotte), tang0097@umn.edu (W. Tang), hanso047@umn.edu (N. Hanson), mdm608@northwestern.edu (M. McDermott), mcriqui@ucsd.edu (M. Criqui), mallison@ucsd.edu (M. Allison).

Conflict of Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Appendix

Additional Supporting Information may be found in the appendix:

Table S1. Adhesion molecules assays characteristics.

Table S2. Unadjusted mean ± SD protein levels by ABI category.

Table S3. Cellular adhesion protein correlations (Pearson coefficients).

Figure S1. Subject selection.

association of cellular adhesion molecules with ankle-brachial index (ABI) and ABI category (≤1.0 vs. >1.0) in a diverse population, fifteen adhesion proteins were measured in the Multi-Ethnic Study of Atherosclerosis (MESA). To assess multivariable associations of each protein with ABI and ABI category, linear and logistic regression was used, respectively. Among 2364 participants, 23 presented with poorly compressible arteries (ABI>1.4) and were excluded and 261 had ABI ≤1.0. Adjusting for traditional risk factors, elevated levels of soluble P-selectin, Hepatocyte Growth Factor and Secretory Leukocyte Protease Inhibitor were associated with lower ABI (P = .0004, .001 and .002, respectively). Per each standard deviation of protein, we found 26%, 20%, and 19% greater odds of lower ABI category (P = .001, .01 and .02, respectively).. Further investigation into the adhesion pathway may shed new light on biological mechanisms implicated in PAD.

Keywords

ankle-brachial index; hepatocyte growth factor; P-selectin; peripheral artery disease; secretory leukocyte protease inhibitor

Introduction

Peripheral artery disease (PAD) affects approximately 8.5 million Americans over the age of 40.[1] The vast majority of PAD patients are asymptomatic and the most commonly used diagnostic tool is the ankle-brachial index (ABI), a ratio comparing ankle with arm systolic blood pressures. Although PAD is traditionally defined by an ABI of less than 0.90, a large meta-analysis indicated that ABI values between 0.91 and 1.0 were associated with increased cardiovascular disease (CVD) mortality compared to ABI > 1.0.[2] Within the Multi-Ethnic Study of Atherosclerosis (MESA), ABI <1.0 was significantly associated with incident CVD and with prevalence of subclinical atherosclerosis.[3, 4] An ABI ≤ 1.0 reflects a reduced blood pressure in the legs, primarily due to atherosclerotic plaques partially obstructing the arterial lumen. As atherosclerosis is a systemic disease, individuals with PAD are more likely to present with concomitant coronary and carotid atherosclerosis.[4-6] Consequently, low ABI can be considered a marker of overall atherosclerotic burden and is a strong predictor of cardiovascular and all-cause mortality.[7]

Inflammation plays a pivotal role in the initiation and progression of PAD.[8, 9] Elevated levels of inflammatory markers are associated with increased incidence, severity, and prognosis of PAD, independent of traditional risk factors.[10-13] In contrast, a previous study conducted in MESA found a limited association between inflammation and PAD.[14] However, the cellular adhesion pathway has been associated with PAD in multiple reports[10, 13, 15, 16] and includes molecules such as intercellular and vascular adhesion molecules (ICAM-1 and VCAM-1); proteins of the Selectin family, as well as a variety of secretory proteins with regulatory functions.

While previous cohort studies have explored the association of inflammatory biomarkers belonging to different biological pathways with various cardiovascular endpoints,[17-19] only a limited number of proteins in the adhesion pathway, namely ICAM-1 and VCAM-1, have been studied in the context of longitudinal studies investigating PAD risk.[10, 15, 20]

Furthermore, studied populations were predominantly white. Based on prior evidence provided by *in vitro* and *in vivo* studies, we selected a panel of soluble cellular adhesion pathway proteins that have been shown to have a role in atherosclerosis, and we tested their association with ABI and ABI category in a large, multi-ethnic population. A comprehensive assessment of the relationship between novel and known components of the cellular adhesion pathway and PAD in a multi-ethnic population may shed new light on the importance of this particular phase of inflammation in cardiovascular disease.

Methods

Study Population

MESA enrolled African, Chinese, Hispanic, and non-Hispanic white Americans, with no history of CVD in order to investigate subclinical and clinical CVD in a large and diverse population. MESA has been described in detail elsewhere[21] and information regarding data access is available on the MESA website (www.mesa-nhlbi.org). In order to measure a large number of circulating adhesion proteins in a representative sample of the MESA population, a stratified random sample including 720 individuals for each of the four races/ethnicities was used (n = 2880). This subgroup was randomly generated from Exam 1 participants who gave consent for DNA sample use (as shown in Figure S1).

Fifteen adhesion proteins were measured in samples obtained at Exam 2 (2002-2004). Plasma was available for 2574 participants and, of those; serum was available for 2441 participants. Among these, 34 individuals were excluded due to CVD events prior to Exam 2, 1 due to cognitive impairment, and 3 individuals were excluded due to inconsistencies between the field center where they were enrolled and their self-reported race/ethnicity. Thus, the final sample size was 2536 for plasma and 2403 for serum proteins. MESA and its ancillary studies were approved by the Institutional Review Board at participating centers and all participants gave written informed consent.

Soluble Protein Measurements

Quantitative sandwich enzyme-linked immunosorbent assays (ELISA) were used to measure soluble proteins. Chemokine ligand 21 (CCL21), hepatocyte growth factor (HGF), interleukine-2 soluble receptor (IL-2sr), matrix metalloproteinase 1 (MMP-1), matrix metalloproteinase 2 (MMP-2), secretory leukocyte protease inhibitor (SLPI), E-Cadherin, intercellular adhesion molecules 1 (ICAM-1), L-selectin, vascular cell adhesion molecule 1 (VCAM-1), and tissue inhibitor of metalloproteinases 2 (TIMP-2) were measured in serum, while P-selectin, regulated on activation normal T cell expressed and secreted (RANTES), stromal derived factor 1α (SDF-1α) and transforming growth factor β1 (TGFβ1) were measured in plasma. The inter-assay coefficient of variation and the minimum detectable level for each of the ELISA assays, as well as the specific type of assay used, are summarized in Table S1.

Outcomes and Covariates

The ABI was measured at Exam 3 (2004- 2005), using a standardized protocol.[22] Briefly, systolic blood pressure was measured in both the left and right brachial, dorsalis pedis, and

posterior tibial arteries using a hand-held Doppler instrument with a 5-mHz probe. The ABI was calculated for both the left and right sides as maximum systolic blood pressure in the posterior tibial artery and dorsalis pedis, divided by the average of the left and right brachial pressures. In the event that left and right brachial pressures differed by 10 mmHg or more, the higher of the brachial pressures was used. If a pulse was detected when the cuff was inflated to 300 mmHg, the ABI was classified as "incompressible." For these analyses, minimum of the left and right leg ABI was used. However, we also examined associations with the ABI defined by first excluding those with ABI > 1.4 in either leg, then using the minimum of the left and right leg ABI. ABI (continuous) and ABI category (defined as ABI ≤ 1.0 vs ABI > 1.0 according to previous findings that ABI values between 0.91 and 1.0 were associated with increased cardiovascular mortality compared to ABI > 1.0 [2]) were used as outcome variables.[2]

Concurrently, detailed information on demographics, past medical history, medications and risk factors was collected through a combination of self-administered and interview-administered questionnaires. Body mass index (BMI) was calculated as weight (kg)/height^2 (m^2). Resting seated blood pressure was measured three times and the average of the second and third readings was used in the analyses. Hypertension was as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or use of anti-hypertensive medications.[23] Diabetes was defined as any participant who self-reported a physician diagnosis, used diabetic medication, or had a fasting glucose ≥ 126 mg/dL. Triglycerides were measured in plasma by a glycerol blanked enzymatic method and cholesterol was measured in plasma using a cholesterol oxidase method. HDL cholesterol was measured by the cholesterol oxidase method after precipitation of non-HDL-cholesterol with magnesium/dextran. LDL-cholesterol was calculated in specimens having a triglyceride < 400 mg/dL via the Freidewald equation. Glomerular Filtration Rate (GFR) was estimated using the Chronic Kidney Disease (CKD) Epidemiology Collaboration formula.[24]

Statistical Analysis

Univariate associations of population characteristics and of each protein with ABI category were assessed by t-test, Wilcoxon-Mann-Whitney, or chi-square test as appropriate, and with ABI using linear regression. ABI was approximately normally distributed, so no transformations were used in analysis. All adhesion proteins were modeled per standard deviation (SD) after verifying there were no departures from linearity using generalized additive models (GAMs) with a smoother that fits cubic B-splines. To assess multivariable associations of each protein with the ABI, linear regression was used; for ABI category (ABI ≤ 1.0, ABI > 1.0), logistic regression was used. In both analyses, participants with ABI > 1.4 were excluded. Staged models were used to assess potential covariates and confounders. The first model consisted of age, sex, field site, and race/ethnicity as adjusting covariates; in the fully adjusted model BMI, ever smoking, diabetes and hypertension status, eGFR, HDL and LDL cholesterol, and triglycerides were added.

Results

Population Characteristics

Among 2536 participants, 172 had missing values for ABI at Exam 3 and 23 presented with poorly compressible arteries (ABI > 1.4). Of the remaining 2341, 261 had an ABI ≤ 1.0, and 79 of these had an ABI ≤ 0.90. Table 1 shows population characteristics for ABI category. Significant differences were found for age, sex, and race/ethnicity between the two groups; participants with ABI ≤ 1.0 were more likely to be females, older, and African American compared to participants with ABI > 1.0. Furthermore, those with ABI ≤ 1.0 were more likely to have any history of smoking, diabetes, and/or hypertension, and have CKD, although mean eGFR was similar in the two groups suggesting that the majority of patients had mild CKD. As shown in Table 2 and Table S2, mean levels of the majority of adhesion proteins were significantly higher in those with ABI ≤ 1.0. Correlation coefficients for adhesion proteins are shown in Table S3.

Adhesion Proteins and ABI

Soluble P-selectin, HGF, and SLPI were significantly associated with ABI (Table 3). In the fully adjusted model, each SD higher levels of soluble P-selectin, or SLPI was associated with a lower value for ABI of 0.008 ($P = .0004$ and .002, respectively); each SD higher levels of soluble HGF with lower ABI level of 0.009 ($P = .001$). Among matrix metalloproteinases, MMP-1 was associated with ABI; specifically, ABI was 0.005 lower per each SD higher MMP-1 levels ($P = .05$). The same reduction in ABI was observed in the fully adjusted model for each SD higher levels or RANTES ($P = .02$). Among other circulating factors involved in the adhesion pathway, significant results were obtained for TGF-β1, and IL-2sr (Adjusted $\beta = -0.005$, $P = .02$; Adjusted $\beta = -0.005$, $P = .04$, respectively). Soluble L-selectin showed an inverse association in the unadjusted model only; for each SD higher levels of soluble L-selectin levels, ABI was higher by 0.005 ($P = .03$). Similarly, E-cadherin was directly associated with ABI only in the unadjusted model ($\beta = -0.006$, $P = .007$). The additional adjustment for the number of pack-years in ever smokers did not significantly modify these associations (data not shown).

To assess race/ethnic heterogeneity, a formal interaction model adjusting for age, sex, and field site was used. A significant interaction was observed for HGF ($P = .004$). In minimally adjusted models, among African Americans, the association of HGF with the ABI was significant ($P < .001$) but not for non-Hispanic whites ($P = .20$), Chinese ($P = .97$), and Hispanic ($P = .25$) Americans. In fully adjusted models however, the association of HGF with the ABI was significant for both non-Hispanic whites ($P = .04$) and African ($P < .001$), but not among Chinese ($P = .54$) and Hispanic ($P = .96$) Americans. There were no significant interactions for any other adhesion protein by race/ethnicity for the ABI (all $P > .10$). Similar results were obtained in the sensitivity analysis utilizing a slightly different method to derive the ABI (excluding patients with ABI > 1.4 in either leg then using the minimum of the left and right ABI).

Soluble Adhesion Proteins and Ankle Brachial Index Categories

In the fully adjusted model, including age, sex, race/ethnicity, field center, CKD and traditional CVD risk factors, HGF, P-selectin and SLPI were associated with ABI ≤ 1.0. Each SD increase in HGF was associated with 20% greater odds of ABI ≤ 1.0 compared to ABI > 1.0 (95% confidence interval [CI] 1.04-1.39; $P = .01$). Similarly, a 26% and a 19% greater odds of ABI ≤ 1.0 were found per one SD increase in P-selectin and SLPI, respectively (95% CI, 1.10-1.46; $P = .001$ and 95% CI, 1.03-1.37; $P = .02$) as shown in Table 3. In addition, RANTES and IL-2sr were associated with ABI ≤ 1.0. In particular, the adjusted OR (95% CI) were 1.14 (1.01-1.28); $P = .03$ for RANTES; and 1.15 (1.01-1.30), $P = .04$ for IL-2sr. Finally, E-cadherin was only associated with ABI ≤ 1.0 in the minimally adjusted model including age, sex, race/ethnicity and field center (OR (95% CI) 1.20 (1.06-1.37); $P = .004$). Again, these associations were attenuated but still significant after adjustment for number of pack-years. In models adjusted for age, sex, and field site, there was no evidence of significant interactions of any adhesion protein by race/ethnicity for ABI category (all $P > .20$).

Discussion

In this study, we found a significant association between proteins involved in the adhesion pathway and ABI, independent of traditional cardiovascular risk factors. In particular, we found that higher levels of soluble P-selectin, HGF, SLPI, RANTES and IL-2 are associated with lower ABI and with lower ABI category, independent from traditional cardiovascular risk factors.

P-selectin is expressed on endothelial cells and on platelets during inflammation. Despite the higher levels of soluble P-selectin that were found among PAD patients in case-control studies,[25, 26] previous population studies assessing the association of this protein with PAD or ABI found null results. In particular, in the Framingham Offspring Study, a predominantly white population, soluble P-selectin was not associated with PAD defined using ABI categories or with reported intermittent claudication.[27] Similar results were obtained in a European study conducted by Bennet et al. among African Caribbeans and South Asians;[28] of note, significant differences in soluble P-selectin levels were found in this study among the two races/ethnicities. Both studies defined PAD as ABI < 0.9. In contrast, in our population, soluble P-selectin was associated with both lower levels of ABI and lower ABI category. These inconsistencies might be due to differences in population characteristics, or in the threshold used. Another possible explanation could be that the power to detect an association was limited by the sample size in previous studies. In fact, the number of PAD cases was 111 in the Framingham Offspring [27] population and only 69 in the study by Bennet et al.[28]

HGF is a pleiotropic factor that promotes angiogenesis, among other functions including cell growth regulation, anti-apoptotic effects, and reduction of fibrosis.[29, 30] Recently, the efficacy and safety of gene therapy with HGF have been studied in the context of therapeutic angiogenesis for PAD patients.[31] Gene therapy with HGF was shown to improve ABI, reduce pain, and ischemic ulcer size in patients with critical limb ischemia.[32] In case-control studies, high levels of this protein have been found in individuals with PAD compared to

controls.[33, 34] Similarly, we found that higher levels of HGF are associated with lower ABI and with lower ABI category. While a protective association would have been expected considering the pro-angiogenic activity of this factor, high levels of circulating HGF have been previously associated with diseases of the cardiovascular system, namely stroke,[35] coronary artery disease[36, 37] and heart failure.[38, 39] It has been hypothesized that high HGF levels in patients with chronic CVD represents an adaptive mechanism that is not capable of completely restoring blood flow; or that among the pleiotropic functions of this growth factor some are beneficial and some detrimental for the cardiovascular system.[40] Interestingly, we found significant differences in the association of HGF with ABI among races/ethnicities; in particular, the association between ABI and HGF appeared to be stronger among African Americans.

SLPI is a leukocyte protease inhibitor that reduces ischemia/reperfusion damage due to its anti-inflammatory action. In fact this protein inhibits neutrophil protease and down-regulates other inflammatory proteins.[41, 42] At the same time, this protein is implicated in wound healing and matrix remodeling, as it is an inhibitor of elastase.[43] High levels of SLPI were detected in patients with acute ischemic stroke and were inversely associated with ischemic damage.[44] We report an association of SLPI with lower ABI and with lower ABI category. This could be explained by the chronic activation of inflammatory pathways in these patients, leading to an increase of this inhibiting protein reflecting a failure of the anti-inflammatory mechanisms.

RANTES and IL-2sr were associated with ABI and ABI category, albeit less significantly. RANTES is a chemokine involved in homing of leukocytes to inflammatory sites, while IL-2sr is the soluble form of the receptor for IL-2, a cytokine primarily associated with T-lymphocyte function. These proteins are secreted in response to inflammation, which in turn has a pivotal role in the pathogenesis of PAD.[8] Finally, higher levels of MMP-1, a metalloproteinase, TGF-β1, a multifunctional growth factor regulating immune cells activity, and E-cadherin, an intra-cellular adhesion molecule were associated with lower ABI; the association was attenuated but still significant after adjustment for traditional PAD risk factors. While some evidence exists on the role of these proteins in atherosclerosis,[45-47] they haven't been previously studied in the context of PAD and they have been rarely measured in large and diverse populations.

Interestingly, we found no association between soluble ICAM-1 or VCAM-1 and ABI. In the Physician Health Study, similar results were observed for VCAM-1, but a positive association was found between higher levels of soluble ICAM-1 at baseline and the development of symptomatic PAD during the follow-up period.[15] Similarly, in the Edinburgh Artery Study, higher levels of soluble ICAM-1, but not of VCAM-1, were associated with a reduction in ABI over time.[10] Our results are concordant with findings of the Rotterdam study, where no cross-sectional association was found between the ABI and either protein.[48] It is possible that the levels of soluble ICAM-1 predict PAD development over time and that the cross-sectional nature of this study hindered our ability to detect a significant association. Alternatively, inconsistencies with previous studies may be due to differences in the study population or in the outcome definitions.

The present study has some limitations. First, the proteins were measured at a single point in time and 19 months prior to the measurement of ABI on average; nevertheless, circulating levels of these proteins were shown to be relatively stable over time.[49, 50] Second, some of the measured markers, namely ICAM-1, VCAM-1, E-cadherin, L- and P-selectin, are cell-bound proteins shed upon activation. While it is probable that the soluble levels of these proteins correlate with their expression on the cell surface, this might be an imperfect measure. Third, 15 adhesion proteins were considered in our analysis, posing the problem of multiple comparisons; the scope of this project was to explore novel markers implicated in the pathogenesis of PAD using a pathway approach and a large multi-ethnic population. Further studies are needed to confirm these findings. Finally, given that ABI alone does not reliably diagnose PAD in patients with non-compressible arteries (ABI > 1.4), these participants were excluded, which may have led to missing some PAD cases. Nonetheless, if this misclassification occurred, it biased our estimate towards the null hypothesis making our approach conservative. The strengths of our study include the use of large and diverse population that is well-designed to assess CVD and the focus on protein belonging to the same biological pathway. Due to the adherence to standardized procedures and strict quality controls, the collected data have high validity and reliability.

In this study we have showed the association of a number of novel proteins belonging to the cellular adhesion pathway with ABI and ABI category; in particular, soluble P-selectin, HGF and SLPI are associated with lower ABI and with lower ABI category. This study confirms the association between the cellular adhesion pathway and PAD within a large multi-ethnic population; while adding information on previously studied adhesion proteins, it broadens the current knowledge on this topic to include novel proteins. Further investigation on these promising components of the adhesion pathway is needed to shed new light on biological mechanisms involved in PAD and eventually lead to new tools for defining cardiovascular risk and preventing CVD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Population Characteristics by Ankle-Brachial Index (ABI) Category (Individuals with ABI >1.4 Are Not Included).

Characteristics	ABI ≤1.0 n = 261	ABI >1.0 n = 2080	*P* Value[a]
Age, years	69.0 ± 10.4	63.5 ± 9.7	< .001
Female sex, n (%)	167 (64%)	1084 (52.1)	< .001
Race/Ethnicity, n (%)			
Non-Hispanic whites	66 (25.3)	537 (25.8)	< .001
African Americans	91 (34.9)	478 (23.0)	
Hispanics	53 (20.3)	511 (24.6)	
Chinese Americans	51 (19.5)	554 (26.6)	
Body mass index, kg/m^2	27.1 ± 5.6	28.0 ± 5.5	.02
Ever smokers, n (%)	142 (54.4)	937 (45.1)	.004
Number of pack-years, median (IQR)	0.63 (0-25.8)	0 (0-10.5)	< .001
HDL cholesterol, mg/dl	52.4 ± 15.5	51.1 ± 14.3	.20
LDL cholesterol, mg/dl	107.2 ± 31.2	112.7 ± 31.2	.008
Triglycerides, mg/dl	74 (111, 156)	77 (113, 162)	.52
Lipid lowering medications use, n (%)	79 (30.7)	533 (26.1)	.11
Diabetes mellitus, n (%)	61 (23.4)	316 (15.2)	< .001
Fasting glucose, mg/dL	101.7 ± 31.2	99.0 ± 27.0	.18
Diabetes medication use, n (%)	50 (19.2)	241 (11.6)	< .001
eGFR, ml/min/1.73m^2	71.1 ± 20.0	78.6 ± 16.1	< .001
CKD (eGFR<60), n(%)	72 (27.6)	260 (12.5)	< .001
Hypertension, n (%)	169 (64.8)	922 (44.3)	< .001
Systolic blood pressure, mmHg	127.8 ± 22.5	122.1 ± 19.7	< .001
Diastolic blood pressure, mmHg	68.9 ± 9.8	70.2 ± 9.8	.04
Pulse pressure, mmHg	58.9 ± 19.3	51.8 ± 16.1	< .001

Abbreviations: ABI, ankle-brachial index; IQR, interquartile range; HDL, high density lipoprotein; LDL, low density lipoprotein; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease.

[a] *P* Values by t-test, Wilcoxon or chi-square test as appropriate.

Table 2

Unadjusted Mean ± SD Protein Levels by Ankle-Brachial Index (ABI) Category.

Characteristics	ABI ≤1.0 n = 261	ABI > 1.0 n = 2080	*P* Value[a]
CCL-21, pg/mL	902 ± 293	789 ± 271	< .001
E-cadherin, ng/mL	238 ± 80	222 ± 62	.003
HGF, pg/mL	1,054 ± 260	973 ± 250	< .001
ICAM-1, ng/mL	266 ± 108	258 ± 118	.30
IL-2sr, pg/mL	808 ± 453	707 ± 327	< .001
L-selectin, ng/mL	876 ± 208	895 ± 194	.16
MMP-1, ng/mL	6.2 ± 4.6	5.5 ± 4.1	.02
MMP-2, ng/mL	198 ± 31	195 ± 31	.16
P-selectin, ng/mL	31 ± 9.3	29 ± 9.2	.002
RANTES, pg/mL	4,933 ± 5081	4,211 ± 3,892	.03
SDF-1α, pg/mL	1,982 ± 480	1,935 ± 441	.11
SLPI, pg/mL	49,755 ± 12853	45,775 ± 10,457	< .001
TGFβ-1, pg/mL	4,259 ± 2431	3,911 ± 2,284	.02
TIMP-2, ng/mL	82 ± 12	81 ± 12	.05
VCAM-1, ng/mL	768 ± 222	728 ± 222	.008

Abbreviations: ABI, ankle-brachial index; CCL21, chemokine ligand 21; HGF, hepatocyte growth factor; ICAM-1, intercellular adhesions molecule 1; IL-2SR, interleukin 2 soluble receptor; MMP-1, matrix metalloproteinase 1; MMP-2, matrix metalloproteinase 2; RANTES, regulated on activation normal T cell expressed and secreted; SDF-1α, stromal derived factor 1α; SLPI, secretory leukocyte protease inhibitor; TGFβ-1, transforming growth factor; TIMP-2, tissue inhibitor of metalloproteinases 2; VCAM-1, vascular cell adhesion molecule 1.

[a] *P* Values by t-test or Wilcoxon test as appropriate.

Table 3

Adjusted Association of Adhesion Proteins with ABI and with ABI Category.

	Ankle-brachial index (ABI)				ABI ≤ 1.00 vs ABI > 1.00			
Adhesion protein	**Model 1[a] Beta[c] (SE)**	***P* Value**	**Model 2[b] Beta[c] (SE)**	***P* Value**	**Model 1[a] OR (95% CI)**	***P* Value**	**Model 2[b] OR (95% CI)**	***P* Value**
CCL-21	−0.003 (0.003)	.30	−0.0004 (0.003)	.86	1.10 (0.96-1.26)	.19	1.04 (0.89-1.21)	.61
E-cadherin	−0.006 (0.002)	**.007**	−0.004 (0.003)	.12	1.20 (1.06-1.37)	**.004**	1.13 (0.97-1.30)	.12
HGF	−0.005 (0.002)	**.05**	−0.009 (0.003)	**.001**	1.19 (1.04-1.37)	**.01**	1.20 (1.04-1.39)	**.01**
ICAM-1	−0.003 (0.002)	.15	−0.004 (0.002)	.13	1.03 (0.93-1.21)	.37	1.05 (0.91-1.20)	.54
IL-2sr	−0.007 (0.002)	**.005**	−0.005 (0.003)	**.04**	1.20 (1.06-1.35)	**.003**	1.15 (1.01-1.30)	**.04**
L-selectin	0.005 (0.002)	**.03**	0.003 (0.002)	.19	0.95 (0.82-1.10)	.46	0.72 (0.54-0.97)	.03
MMP-1	−0.004 (0.002)	**.05**	−0.005 (0.002)	**.05**	1.08 (0.95-1.22)	.24	1.08 (0.94-1.23)	.28
MMP-2	−0.001 (0.002)	.69	0.0001 (0.002)	.94	0.94 (0.82-1.09)	.43	0.91 (0.79-1.06)	.21
P-selectin	−0.010 (0.002)	**< .0001**	−0.008 (0.002)	**.0004**	1.28 (1.11-1.46)	**.0004**	1.26 (1.10-1.46)	**.001**
RANTES	−0.005 (0.002)	**.02**	−0.005 (0.002)	**.02**	1.13 (1.01-1.27)	**.04**	1.14 (1.01-1.28)	**.03**
SDF-1b	0.0008 (0.002)	.74	0.0007 (0.002)	.75	0.97 (0.85-1.11)	.65	0.95 (0.82-1.09)	.46
SLPI	−0.011 (0.002)	**< .0001**	−0.008 (0.003)	**.002**	1.26 (1.10-1.43)	**.0006**	1.19 (1.03-1.37)	**.02**
TGF-β1	−0.005 (0.002)	**.05**	−0.005 (0.002)	**.02**	1.10 (0.97-1.25)	.12	1.12 (0.98-1.28)	.09
TIMP-2	0.003 (0.002)	.18	0.003 (0.003)	.15	0.93 (0.80-1.07)	.30	0.90 (0.77-1.05)	.19
VCAM-1	−0.002 (0.002)	.31	−0.0005 (0.002)	.83	1.07 (0.93-1.24)	.32	1.02 (0.88-1.18)	.82

Abbreviations as in Table 2.

[a] Minimally adjusted model including age, sex, race/ethnicity and field site.

[b] Fully adjusted model including Model 1+ BMI, ever smoking, diabetes, hypertension, estimated Glomerular Filtration Rate (eGFR), triglycerides, LDL, HDL and total cholesterol.

[c] Beta coefficients represent the difference in ABI for each SD increase in adhesion proteins.