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ORIGINAL RESEARCH

Femoral Artery Atherosclerosis Is Associated With Physical Function Across the Spectrum of the Ankle-Brachial Index: The San Diego Population Study

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***Background*—**The ankle-brachial index (ABI) is inadequate to detect early-stage atherosclerotic disease, when interventions to prevent functional decline may be the most effective. We determined associations of femoral artery atherosclerosis with physical functioning, across the spectrum of the ABI, and within the normal ABI range.

***Methods and Results*—**In 2007–2011, 1103 multiethnic men and women participated in the San Diego Population Study, and completed all components of the summary performance score. Using Doppler ultrasound, superficial and common femoral intima media thickness and plaques were ascertained. Logistic regression was used to assess associations of femoral atherosclerosis with the summary performance score and its individual components. Models were adjusted for demographics, lifestyle factors, comorbidities, lipids, and kidney function. In adjusted models, among participants with a normal-range ABI (1.00–1.30), the highest tertile of superficial intima media thickness was associated with lower odds of a perfect summary performance score of 12 (odds ratio=0.56 [0.36, 0.87], *P*=0.009), and lower odds of a 4-m walk score of 4 (0.34 [0.16, 0.73], *P*=0.006) and chair rise score of 4 (0.56 [0.34, 0.94], *P*=0.03). Plaque presence (0.53 [0.29, 0.99], *P*=0.04) and greater total plaque burden (0.61 [0.43, 0.87], *P*=0.006) were associated with worse 4-m walk performance in the normal-range ABI group. Higher superficial intima media thickness was associated with lower summary performance score in all individuals (*P*=0.02).

***Conclusions*—**Findings suggest that use of femoral artery atherosclerosis measures may be effective in individuals with a normal-range ABI, especially, for example, those with diabetes mellitus or a family history of peripheral artery disease, when detection can lead to earlier intervention to prevent functional declines and improve quality of life. **(*J Am Heart Assoc*. 2017;6:e005777. DOI: 10.1161/JAHA.117.005777.)**

Key Words: atherosclerosis • coagulation • inflammation • peripheral artery disease • physical function • plaque

Globally, over 200 million people live with peripheral artery disease (PAD),[1] with ≈8.5 million people affected in the United States alone.[2] The associated comorbidities and surgical procedures because of PAD result in significant cost, both in terms of quality of life and dollars.[3] Of individuals with PAD, the majority are either asymptomatic (40%) or do not exhibit classic symptoms of leg claudication (50%), leaving only 10% who exhibit classic claudication symptoms.[4,5] Even when asymptomatic, PAD is associated with decreased functional status, mobility, and quality of life, including the inability to walk one quarter mile, climb 1 flight of stairs, or complete a 6-minute walk.[6]

In population-based studies including those with and without PAD (ankle-brachial index [ABI] ≤0.90), the ABI has been associated with measures of functional status and physical function,[7–9] as well as declines in physical function

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Clinical Perspective

What Is New?

- In a multiethnic population-based study of predominantly healthy older men and women, presence of femoral artery atherosclerosis was significantly associated with worse physical function, extending previous findings in those with peripheral artery disease.
- Even among participants with a normal-range ankle-brachial index (1.00–1.30), higher levels of the superficial femoral artery intima media thickness and plaque presence were significantly associated with worse physical performance.
- Associations of femoral artery atherosclerosis and physical function did not appear to be mediated by inflammatory or coagulation biomarkers in this study.

What Are the Clinical Implications?

- Findings suggest that even early stages of femoral artery atherosclerosis are associated with changes in physical performance.
- While it may be prohibitive to screen all patients with a normal ankle-brachial index for femoral atherosclerosis, it could be beneficial for early detection in individuals with a normal ankle-brachial index and other comorbidities such as type 2 diabetes mellitus or a family history of peripheral artery disease.
- Femoral artery atherosclerosis measures may be especially effective in those who have a normal-range ankle-brachial index and who are likely asymptomatic, when detection can lead to earlier intervention (ie, lifestyle changes or initiation or intensification of statin treatment), to prevent functional declines.

over time.[10] However, the ABI is inadequate for detecting early-stage lower extremity atherosclerotic disease, when intervention efforts to prevent functional decline, associated comorbid conditions, and mitigate the high risk of mortality, may be most effective. By the time ABI progresses into the abnormal range (≤0.90), significant lower extremity disease is typically present[11] (ie, stenosis >50%), providing less opportunity for effective intervention.

Among individuals with PAD, the presence and characteristics of superficial femoral artery plaques have been associated with poorer physical function,[12,13] even after adjustment for levels of the ABI. However, femoral artery measures of atherosclerosis could also provide a path to earlier intervention in individuals without PAD and a normal range (ie, 1.00–1.30) or borderline (0.91–0.99) ABI, especially among those with a normal ABI and significant comorbidities or family history of PAD, or in detection of those with asymptomatic PAD. This in turn could lead to prevention of functional decline and improved quality of life.

In a population-based, multiethnic cohort of men and women, we examined the associations of common and superficial femoral artery intima media thickness (IMT) and atherosclerotic plaque presence and frequency with the summary performance score (SPS) and its components, across the range of the ABI, as well as in a subset with a normal-range ABI. Additionally, as inflammation and coagulation play a significant role in lower extremity subclinical atherosclerosis,[14–18] we determined whether circulating levels of inflammation and coagulation markers mediated the associations of femoral artery atherosclerosis and the SPS.

Methods

Study Participants

The San Diego Population Study is a prospective cohort of ethnically diverse men and women designed to study lower extremity PAD and venous disease. The follow-up examination took place from 2007 to 2011, when 1103 participants returned an average of 11 years after their first clinical examinations in 1994–1998. Participants were current or former employees of the University of California—San Diego or significant others of these employees, who resided in San Diego County. Participants were then chosen randomly within age, race/ethnic and sex strata, resulting in the cohort of ≈65% women, and 60% non-Hispanic white, 13% black, 15% Hispanic, and 12% Asian. Women and racial/ethnic minorities (black, Hispanic, Asian) were oversampled in order to have adequate power for hypotheses involving these groups. The current study includes the 1103 participants from the follow-up examination in 2007–2011. Further details of the study have been published elsewhere.[19–21]

For all study procedures, participants provided signed informed consent after a detailed introduction and description of the study at both the baseline and follow-up examinations. The study received approval from the Institutional Review Board Committee on Investigations Involving Human Subjects at University of California-San Diego.

Ankle-brachial index

With the participant in a supine position, systolic blood pressure was measured twice in both arms. Continuous-wave Doppler ultrasound (Acuson Aspen, Seimens, Inc) was used to measure systolic blood pressure twice in both the anterior and posterior tibial arteries. The ABI for each side was calculated as the maximum of the average systolic blood pressure of the posterior tibial or dorsalis pedis divided by the maximum of the average of the left and right arm systolic blood pressure. The higher arm systolic blood pressure was

used in these calculations because of previous studies showing a strong association between PAD and subclavian stenosis.[22] The overall ABI was defined as the lower of the left and right ABI.

Femoral Artery Atherosclerosis

Doppler ultrasound (Acuson Aspen, Seimens, Inc) was used to image the left and right superficial and common femoral arteries in 10-mm segments at an angle of insonation of 90 degrees. Two segments each on the left and right legs were obtained: (1) at the common femoral artery as it emerged from under the inguinal ligament proximal to its bifurcation into the profunda and superficial femoral branches, and (2) at the superficial femoral artery distal to the bifurcation.

Carotid Analyzer software from the Vascular Research Tools 5 Suite (Medical Imaging Applications, LLC, Coralville, IA) was used by trained ultrasound technicians to measure the IMT, as well as to determine plaque presence and frequency. Quality control monitoring was performed at regular intervals throughout the study, using the ultrasound images from 10 to 20 participants. Both inter- and intrareader intraclass correlations generally were >80% for common femoral IMT, and >75% for superficial femoral IMT. In particular, intrareader intraclass correlations were >95% for both the superficial and common femoral IMTs. Spearman correlations for both inter- and intrareader were >0.89 for common femoral IMT, and >0.70 for superficial femoral IMT.

As the far (posterior) arterial wall provided the best images with the least amount of noise, the common and superficial femoral IMTs were calculated as the average of the far wall of both the left and right leg femoral arteries to ensure the lowest possible measurement error. IMTs were calculated even when plaque was present in the segment. Plaque presence was defined by the Mannheim consensus as a focal structure encroaching into the arterial lumen at least 0.50 mm or 50% greater thickness relative to the surrounding IMT, or thickness >1.5 mm as measured from the media-adventitia border to the intima-lumen border.[23,24] For some arterial segments, clear visualization of plaques was limited because of the presence of artifact, and these plaques were classified as probable plaques. Otherwise, participants were classified as having a definite plaque or no visible plaque.

Summary Performance Score

Participants completed the 3 component measures of the SPS, including time to rise from a seated position 5 times, the standing balance, and usual 4-m walking velocity.[25] Each component was scored from 0 and 4; a 0 on a component corresponds to an inability to complete that component, while a 4 corresponds to the best performance. The 3 component scores were summed to calculate the overall SPS, which ranged from 0 to 12. The scale was derived from normative data in 6534 community-dwelling older men and women participating in the Established Populations for the Epidemiologic Study of the Elderly.[25]

Covariates

Age, sex, race/ethnicity, presence of osteoarthritis, and current and past cigarette smoking habits were ascertained via questionnaire. Smoking was defined as ever having smoked versus never smoked. Height (in centimeters) and weight (in kilograms) were measured, and the body mass index was calculated as kg/m^2. A medication inventory was conducted to obtain information on a variety of medications, including statins, as well as diabetes mellitus or hypertension medication use. Diabetes mellitus was defined as self-report, or use of antidiabetic medications or insulin. Systolic and diastolic blood pressures were measured in the right arm for each participant after 5 minutes of rest. Hypertension was defined as a systolic pressure ≥140 mm Hg or a diastolic pressure ≥90 mm Hg, or use of antihypertensive medications. Cardiovascular disease, including previous myocardial infarction, stroke, angioplasty, or revascularization, was also assessed via self-report questionnaire.

Nonfasting blood samples were collected, stored at −80°C, and transferred to a laboratory where they were analyzed within 24 hours. Direct enzymatic assays were used to determine total and high-density lipoprotein cholesterol on the Roche Cobas 6000 analyzer (Roche Diagnostics Corporation, Indianapolis, IN).[26] Low-density lipoprotein cholesterol was estimated using the Friedewald equation.[27] Dyslipidemia was defined as a ratio of total cholesterol to high-density lipoprotein cholesterol >5.0 or statin use, which has consistently been found the best single lipid/lipoprotein parameter in assessing cardiovascular disease risk,[28] or use of lipid-lowering medications at baseline. Serum creatinine levels were calibrated to the isotope dilution mass spectrometry standard and measured using a Roche Cobas 6000 analyzer (Roche Diagnostics Corporation, Indianapolis, IN). Estimated glomerular filtration rate was calculated with the CKD-Epi equation.[29]

Inflammation and Coagulation Markers

C-reactive protein (CRP) and fibrinogen were measured in EDTA plasma, and lipoprotein-a was measured in serum, using nephelometric assays on a BNII System (Siemens Healthcare, Erlange, Germany). The ranges of interassay coefficients of variation for CRP, fibrinogen, and lipoprotein-a were 4.1% to 5.1%, 3.2% to 4.7%, and 5.2% to 8.2%, respectively. Intercellular adhesion molecule-1 and pentraxin-3 were measured in

EDTA plasma using ELISA (R&D Systems, Minneapolis, MN), with coefficient of variation ranges of 10.3% to 11.0% and 9.3% to 14.9%, respectively. Intercellular adhesion molecule-1 was measured using a nonallele-specific assay. Interleukin (IL)-6 was measured in serum, also via ELISA (R&D Systems, Minneapolis, MN), with a coefficient of variation range of 4.2% to 6.3%. D-dimer was measured in EDTA plasma on the Evolution Coagulation Analyzer (Diagnostica Stago, Parsippany, NJ), with a coefficient of variation range of 2.7% to 24.7%.

Statistical Analysis

Univariate associations of superficial femoral artery IMT tertiles and participant characteristics were conducted using ANOVA, χ^2, or Kruskal–Wallis as appropriate. Superficial and common femoral artery IMT were modeled both as continuous per SD, as well as tertiles. Any plaque presence was defined as participants with definite or probable plaques versus no plaques in any 1 of the 4 arterial segments: left superficial, right superficial, left common or right common femoral arteries. Total number of plaques (definite+probable plaques) was obtained by summing the number of plaques across the 4 arterial segments, and modeled as a continuous variable. Because of the large proportion of participants with a perfect score of 12 (73%), SPS was modeled as a binary outcome (12 versus <12). Logistic regression was employed to examine the association of each femoral artery atherosclerosis measure separately with the SPS, with staged model adjustment to determine potential confounders. Final models were adjusted for age, sex, race/ethnicity, body mass index, ever smoking, hypertension, diabetes mellitus, estimated glomerular filtration rate, dyslipidemia, osteoarthritis, and cardiovascular disease. Additionally, separate analyses were also performed using logistic regression, for the 3 SPS subscales (chair rises, standing balance, and 4-m walk), with 4 versus <4 as the binary outcomes. Analyses were conducted among all participants, and also stratified by ABI categories. Participants with symptomatic PAD (ie, with a previous leg angioplasty or revascularization at either the baseline or follow-up examinations) were excluded from analyses including normal or borderline range ABI groups, regardless of their postprocedure ABI.

To determine whether inflammation and coagulation biomarkers mediated the associations between femoral artery atherosclerosis measures and the SPS, analyses were conducted using the mediate function in the mediation package in R Version 3.3.1 following the methods described by Imai et al[30] for linear and nonlinear relationships. CRP, fibrinogen, IL-6, pentraxin-3, lipoprotein-a, D-dimer, and intercellular adhesion molecule-1 were modeled as continuous variables and each was considered separately as mediating factors. Models were adjusted for age, sex, and race/ethnicity, as well as these demographics plus body mass index, ever smoking, hypertension, diabetes mellitus, estimated glomerular filtration rate, dyslipidemia, osteoarthritis, and cardiovascular disease.

Results

A total of 1062 participants had available data on the superficial femoral artery, and 1021 had available data on the common femoral artery, while plaque presence was available on 1065. The mean±SD for superficial femoral IMT was 0.59±0.12 mm and 0.87±0.46 mm for the common femoral segment. Approximately 26% (273/1065) of participants had plaque present, with a mean±SD number of plaques across all segments of 0.39±0.76. The overall average SPS was 11.2±1.9, with 73% of participants having a perfect SPS of 12.

Participants differed significantly across tertiles of superficial femoral artery IMT in all traditional cardiovascular risk factors with the exceptions of low-density lipoprotein cholesterol, diastolic blood pressure, and diabetes mellitus (Table 1). Additionally, participants only marginally differed with regard to the continuous ABI across tertiles of superficial femoral IMT (P=0.11); however, the univariate association of ABI categories with superficial femoral IMT tertiles was significant (P=0.001). Participants also had higher levels of IL-6 (P<0.001) and pentraxin-3 (P=0.01) with increasing tertile of superficial femoral IMT, but did not differ significantly for the other markers of inflammation or coagulation (Table 1).

Figure 1 displays the average superficial and common femoral IMT, as well as average number of plaques by femoral artery segment across ABI categories. Common femoral IMT and mean number of plaques have a distinct U-shaped relationship across ABI categories. Compared to the low (≤0.90) and high (>1.30) ABI categories, superficial femoral IMT was decreased somewhat in the borderline and normal ABI categories (0.91–0.99 and 1.00–1.30). Number of superficial femoral plaques also shows a U-shaped relationship across ABI categories, but this was less pronounced than for common femoral IMT and plaques.

In models adjusted for demographic, lifestyle, and comorbid conditions, each SD greater superficial femoral IMT was associated with significantly lower odds (odds ratio=0.82, 95% CI [0.69, 0.97], P=0.02) of having a perfect SPS of 12 (Table 2). These results were similar when restricting the range of the ABI to 0.91 to 1.40 or 1.00 to 1.30. Further, participants in the highest tertile of superficial femoral IMT (≥0.61 mm) had much lower odds (0.56 [0.38–0.84], P=0.005) of having a perfect SPS of 12, compared with those in the lowest tertile (0.24–0.56 mm) of the superficial

Table 1. Participant Characteristics by Tertiles of Superficial Femoral IMT

	Tertile 1 ≤0.555 mm	Tertile 2 0.556 to 0.608 mm	Tertile 3 >0.608 mm	*P* Value
Age, y*	68±9	71±10	73±10	<0.001
Female sex†	289 (79%)	245 (70%)	176 (51%)	<0.001
Race/ethnicity†				
Non-Hispanic white	206 (56%)	217 (62%)	222 (64%)	0.04
Black	57 (16%)	46 (13%)	50 (14%)	
Hispanic	44 (12%)	38 (11%)	48 (14%)	
Asian	58 (16%)	48 (14%)	28 (8%)	
Ever smoker†	116 (32%)	100 (29%)	139 (40%)	0.005
Body mass index, kg/m^2*	26±5	27±5	28±6	<0.001
Systolic BP, mm Hg*	127±19	131±19	134±18	<0.001
Diastolic BP, mm Hg*	74±10	76±10	75±11	0.23
HDL cholesterol, mg/dL*	65±22	60±19	56±21	<0.001
LDL cholesterol, mg/dL*	111±32	109±33	109±39	0.62
Estimated GFR, min/mL per 1.73 m^2*	81±17	77±16	76±19	<0.001
Osteoarthritis†	82 (23%)	100 (29%)	74 (22%)	0.07
Hypertension†,‡	180 (49%)	223 (64%)	260 (75%)	<0.001
Diabetes mellitus†,‡	29 (8%)	33 (10%)	45 (13%)	0.08
Dyslipidemia†,‡	131 (36%)	147 (42%)	154 (44%)	0.06
Statin use†	99 (28%)	123 (36%)	118 (35%)	0.06
Cardiovascular disease†,‡	19 (5%)	34 (10%)	40 (12%)	0.009
ABI*	1.13±0.12	1.15±0.17	1.14±0.21	0.11
ABI categories†				
≤0.90	7 (2%)	7 (2%)	18 (5%)	0.001
0.91 to 0.99	14 (4%)	12 (4%)	21 (6%)	
1.00 to 1.30	338 (93%)	309 (90%)	286 (83%)	
>1.30	4 (1%)	15 (4%)	18 (5%)	
C-reactive protein, mg/L§	0.94 (0.49, 2.31)	1.14 (0.52, 2.79)	1.24 (0.63, 2.33)	0.09
Interleukin-6, pg/mL§	1.64 (1.01, 2.41)	1.83 (1.22, 2.95)	2.04 (1.39, 2.97)	<0.001
D-dimer, μg/mL§	0.37 (0.23, 0.64)	0.40 (0.23, 0.71)	0.42 (0.26, 0.75)	0.07
Fibrinogen, mg/dL§	380 (329, 430)	380 (340, 428)	387 (337, 433)	0.70
ICAM-1, ng/mL§	334 (283, 415)	344 (286, 415)	355 (298, 420)	0.13
Lipoprotein-a, g/L§	0.11 (0.04, 0.33)	0.11 (0.05, 0.33)	0.13 (0.04, 0.38)	0.72
Pentraxin-3, ng/mL§	1.25 (0.81, 1.90)	1.21 (0.80, 1.69)	1.36 (0.96, 1.94)	0.01

Diabetes mellitus was defined as self-report, or use of antidiabetic medications or insulin. Dyslipidemia was defined as a ratio of total cholesterol to high-density lipoprotein cholesterol (TC/HDL) >5.0 or statin use. Cardiovascular disease was defined as self-report of previous myocardial infarction, stroke, angioplasty, or revascularization. ABI indicates ankle-brachial index; BP, blood pressure; IMT, intima media thickness; GFR, glomerular filtration rate; ICAM-1, intercellular adhesion molecule-1; HDL, high-density lipoprotein; LDL, low-density lipoprotein

*Mean±SD; ANOVA used.

†n (%); χ^2 test used.

‡Hypertension was defined as a systolic pressure ≥140 mm Hg or a diastolic pressure ≥90 mm Hg, or use of antihypertensive medications.

§Median (Q1, Q3); Kruskal–Wallis test used.

femoral IMT. This was similar across the whole range of the ABI, and also when restricting to the normal range of the ABI (Table 2). However, there was no significant association with the overall SPS regarding the common femoral IMT, plaque presence, or plaque number (Table 2). The continuous ABI across the whole range was not significantly associated with a

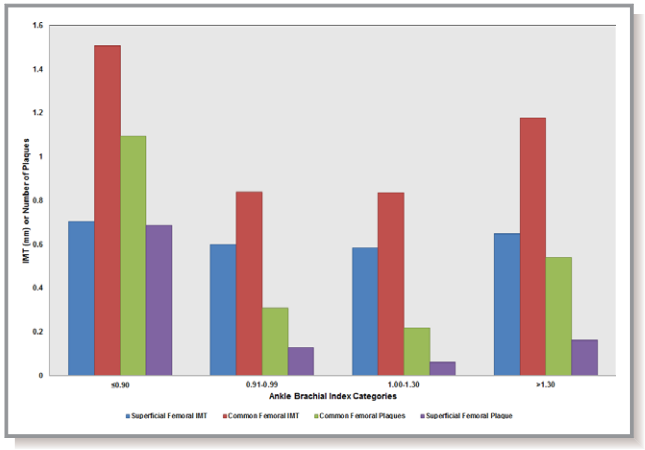

Figure 1. Femoral artery intima media thickness and plaques by ankle-brachial index categories. This figure displays the mean number of plaques (superficial or common femoral) or the mean intima media thickness (superficial and common femoral artery) on the *y*-axis by categories of the ankle-brachial index on the *x*-axis. Blue bars represent the superficial femoral IMT, red bars represent the common femoral IMT, green bars represent common femoral artery plaques, and purple bars represent superficial femoral artery plaques. IMT indicates intima media thickness.

lower odds of an SPS equal to 12 (P=0.72), or when restricting the ABI to 0.91 to 1.40 (P=0.79) or 1.00 to 1.30 (P=0.87).

Among participants with a normal range ABI (1.00–1.30), of the 3 separate components of the SPS (chair rises, standing balance, and 4-m walk), the superficial femoral IMT appeared to exhibit the strongest association with the 4-m walk test (Table 3). Specifically, each SD higher superficial femoral IMT was associated with a significantly lower odds of a perfect score on the 4-m walk (P=0.001). Moreover, participants in the highest tertile of the superficial femoral IMT had a 0.34-fold lower odds of a perfect score on the 4-m walk (P=0.006). These associations were similar, although less strong, for chair rises (Table 3). Additionally, associations of common femoral IMT with the 4-m walk score were marginally significant; participants in tertiles 2 (0.68–0.82 mm) and 3 (>0.82 mm) had approximately half the odds of a perfect 4-m walk score (Table 3), P=0.11, P=0.08, respectively. Among those with a normal ABI (1.00–1.30), participants with any femoral plaque had roughly half the odds (P=0.04) of a perfect 4-m walk score compared with those with no plaques, and each additional plaque corresponded to a 0.61-fold lower odds (P=0.006) of a perfect 4-m walk score (Table 3).

In sensitivity analyses, we modeled plaque presence and total number of plaques with categorization as definite versus probable/no plaque, and results were similar to those in Tables 2 and 3 (data not shown). Additionally, we examined the SPS as a continuous outcome using ANOVA/linear regression, again with similar results (data not shown).

Table 2. Associations of Femoral Artery IMT and Plaques With SPS*

	SPS, 12 vs <12 All Participants, n=1049 OR (95% CI); *P* Value	SPS, 12 vs <12 0.90 < ABI ≤1.40, n=997 OR (95% CI); *P* Value	SPS, 12 vs <12 1.00 ≤ ABI ≤1.30, n=933 OR (95% CI); *P* Value
Common femoral IMT per SD	0.92 (0.80, 1.06); 0.26	0.90 (0.75, 1.07); 0.23	0.90 (0.75, 1.08); 0.25
Superficial femoral IMT per SD	0.82 (0.69, 0.97); 0.02	0.82 (0.67, 0.99); 0.04	0.82 (0.67, 1.01); 0.05
Common femoral IMT			
Tertile 1	Ref	Ref	Ref
Tertile 2	0.75 (0.1, 1.11); 0.15	0.73 (0.49, 1.09); 0.13	0.76 (0.50, 1.15); 0.20
Tertile 3	0.85 (0.57, 1.27); 0.43	0.83 (0.55, 1.25); 0.38	0.89 (0.58, 1.37); 0.59
Superficial femoral IMT			
Tertile 1	Ref	Ref	Ref
Tertile 2	0.80 (0.57, 1.22); 0.34	0.84 (0.56, 1.25); 0.13	0.83 (0.55, 1.25); 0.38
Tertile 3	0.56 (0.38, 0.84); 0.005	0.56 (0.37, 0.84); 0.006	0.56 (0.36, 0.87); 0.009
Plaque presence†	0.86 (0.61, 1.22); 0.40	0.85 (0.59, 1.22); 0.38	0.82 (0.56, 1.21); 0.32
Plaque number‡	0.90 (0.74, 1.09); 0.26	0.88 (0.71, 1.11); 0.29	0.84 (0.66, 1.07); 0.16
ABI	1.03 (0.89, 1.20); 0.71	1.05 (0.75, 1.47); 0.79	0.97 (0.63, 1.47); 0.87

*Models adjusted for age, sex, race/ethnicity, BMI, ever smoking, hypertension, diabetes mellitus, estimated glomerular filtration rate, dyslipidemia, osteoarthritis, and cardiovascular disease. ABI, ankle-brachial index; BMI, body mass index; IMT, intima media thickness; OR, odds ratio; SPS, summary performance score

†Plaque presence in any 1 of the following arterial beds: left or right superficial femoral, left or right common femoral.

‡Summed over all 4 arterial beds: left and right superficial femoral, left and right common femoral.

Table 3. Associations of Femoral Artery IMT and Plaques With SPS Components Among Participants With a Normal-Range ABI*

	Chair Rises, 4 vs <4 OR (95% CI); *P* Value	Standing Balance, 4 vs <4 OR (95% CI); *P* Value	4-m Walk, 4 vs <4 OR (95% CI); *P* Value
Common femoral IMT per SD	1.01 (0.82, 1.24); 0.93	0.96 (0.77, 1.19); 0.70	0.87 (0.67, 1.13); 0.31
Superficial femoral IMT per SD	0.83 (0.66, 1.04); 0.09	0.90 (0.70, 1.15); 0.38	0.65 (0.51, 0.83); 0.001
Common femoral IMT			
Tertile 1	Ref	Ref	Ref
Tertile 2	0.89 (0.55, 1.42); 0.62	0.82 (0.44, 1.54); 0.54	0.55 (0.27, 1.14); 0.11
Tertile 3	1.25 (0.76, 2.07); 0.38	1.12 (0.60, 2.09); 0.73	0.52 (0.24, 1.09); 0.08
Superficial femoral IMT			
Tertile 1	Ref	Ref	Ref
Tertile 2	0.74 (0.46, 1.20); 0.23	0.63 (0.34, 1.17); 0.14	0.63 (0.30, 1.34); 0.23
Tertile 3	0.56 (0.34, 0.94); 0.03	0.52 (0.27, 0.98); 0.04	0.34 (0.16, 0.73); 0.006
Plaque presence†	0.87 (0.56, 1.35); 0.52	1.01 (0.60, 1.70); 0.97	0.53 (0.29, 0.99); 0.04
Plaque number‡	0.81 (0.62, 1.06); 0.12	1.01 (0.73, 1.38); 0.98	0.61 (0.43, 0.87); 0.006

ABI indicates ankle-brachial index; BMI, body mass index; IMT, intima media thickness; OR, odds ratio; SPS, summary performance score.
*Among those with 1.00 ≤ ABI ≤1.30 (n=933); models adjusted for age, sex, race/ethnicity, BMI, ever smoking, hypertension, diabetes mellitus, estimated glomerular filtration rate, dyslipidemia, osteoarthritis, and cardiovascular disease.
†Plaque presence in any 1 of the following arterial beds: left or right superficial femoral, left or right common femoral.
‡Summed over all 4 arterial beds: left and right superficial femoral, left and right common femoral.

In demographic-adjusted analyses, IL-6 appeared to significantly mediate the association of superficial femoral IMT and SPS, as well as components of SPS (Figure 2). This held for analyses among all participants as well as restricted to participants with a normal ABI (1.00–1.30). However, in models adjusted for demographics, lifestyle, and comorbid conditions, IL-6 no longer appeared to be a mediator. In fully adjusted models, among all participants, CRP had marginal significance as a mediator for SPS (P=0.07), standing balance (P=0.08), and was significant for the 4-m walk (P=0.04) (Figure 2). Among those with a normal ABI, in fully adjusted models, CRP had marginal significance as a mediator for the SPS (P=0.12) and the 4-m walk (P=0.10) (Figure 2). Additionally, among those with a normal ABI in fully adjusted models, pentraxin-3 was marginally significant as a mediator for chair rises (P=0.09) (Figure 2). Mediation results for the associations of plaque presence and plaque number with the SPS followed similar patterns (data not shown). Mediation analyses with common femoral IMT were not conducted since the associations with SPS were not statistically significant either overall or in any of the ABI subgroups.

Discussion

In a multiethnic population-based study of predominantly healthy older men and women, we demonstrate that femoral artery atherosclerosis assessed by ultrasound is associated with poorer physical performance, extending previous findings in participants with PAD.[12,13] Across the whole range of the ABI, higher superficial femoral IMT was significantly associated with worse physical performance. Associations of the common femoral IMT with SPS were suggestive based on the magnitudes of the effect, but not statistically significant. Even among participants with a normal-range ABI (1.00–1.30), the highest tertile of superficial IMT remained significantly associated with worse physical performance. Additionally, we observed a U-shaped relationship of IMT and plaques across ABI categories. This is especially of interest for the highest ABI category (>1.30): PAD or subclinical PAD is present at an increased rate in this group, and can be successfully detected in participants with high ABI or incompressible arteries (indicating arterial stiffness) using measures of femoral artery atherosclerosis instead of the ABI. This suggests that atherosclerotic disease, along with arterial stiffness, could be responsible for the increased risk of cardiovascular disease events observed among those with a high ABI.

Further examination of individual SPS components among participants with a normal ABI showed this association was largely driven by associations of higher superficial IMT with worse 4-m walk and chair rise performance. Additionally, both any plaque presence and greater total plaque burden across the superficial and common femoral arteries were significantly associated with worse performance on the 4-m walk in the normal ABI group. Collectively, these data demonstrate that femoral artery ultrasound measures of atherosclerosis are

A

	All Individuals				Among 1.00≤ABI≤1.30			
	SPS	Chair Rises	Standing Balance	Four Meter Walk	SPS	Chair Rises	Standing Balance	Four Meter Walk
Interleukin-6 (pg/mL)	0.002	0.01	0.002	0.005	0.004	0.01	0.01	0.08
C-reactive Protein (mg/L)	0.13	0.18	0.12	0.12	0.52	0.60	0.59	0.56
ICAM-1 (ng/mL)	0.59	0.56	0.58	0.87	0.16	0.13	0.18	0.83
Pentraxin-3 (ng/mL)	0.81	0.74	0.77	0.89	0.18	0.17	0.18	0.80
Fibrinogen (mg/dL)	0.41	0.35	0.43	0.51	0.69	0.67	0.84	0.95
D-dimer (ug/mL)	0.42	0.45	0.48	0.95	0.87	0.88	0.88	0.90
Lp(a)	0.96	0.93	1.00	0.98	0.87	0.85	0.88	0.91

B

	All Individuals				Among 1.00≤ABI≤1.30			
	SPS	Chair Rises	Standing Balance	Four Meter Walk	SPS	Chair Rises	Standing Balance	Four Meter Walk
Interleukin-6 (pg/mL)	0.21	0.21	0.20	0.23	0.22	0.22	0.20	0.25
C-reactive Protein (mg/L)	0.07	0.29	0.08	0.04	0.12	0.44	0.27	0.10
ICAM-1 (ng/mL)	0.95	0.99	0.94	0.94	0.33	0.27	0.32	0.99
Pentraxin-3 (ng/mL)	0.64	0.63	0.61	0.83	0.13	0.09	0.14	0.69
Fibrinogen (mg/dL)	0.28	0.05	0.48	0.32	0.66	0.13	0.85	0.87
D-dimer (ug/mL)	0.38	0.37	0.40	0.87	0.75	0.74	0.83	0.94
Lp(a)	0.97	0.97	0.98	0.93	0.83	0.82	0.91	0.99

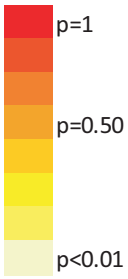

Figure 2. Mediation of the superficial femoral intima media thickness and summary performance score associations by inflammatory and coagulation markers. A, Models adjusted for age, sex, and race/ethnicity, among all participants and those with a normal-range ABI (1.00–1.30). B, Models adjusted for age, sex, race/ethnicity, BMI, ever smoking, hypertension, diabetes mellitus, estimated glomerular filtration rate, dyslipidemia, osteoarthritis, and cardiovascular disease, among all participants and those with a normal-range ABI (1.00–1.30). This figure shows mediation effects of inflammation and coagulation markers on the superficial femoral IMT and SPS among all participants and among those with a normal-range ABI for different levels of model adjustment (A and B). Each cell color represents the significance level of the *P* value, and *P* values are noted in text in each box. *P* values are for the mediation effect of each individual inflammation or coagulation marker on the superficial femoral IMT and SPS (or individual components). ABI indicates ankle-brachial index; BMI, body mass index; ICAM-1, intercellular adhesion molecule-1; IMT, intima media thickness; Lp(a), lipoprotein a; SPS, summary performance score.

associated with worse physical performance even among persons with normal-range ABI measurements.

In a previous study among 457 participants with PAD, the presence of a superficial femoral artery obstruction was significantly associated with worse 6-minute walk time, slower velocity on the 4-m walk, and a lower score on the short physical performance battery.[13] The short physical performance battery is the same scale as the SPS used in our study. Higher mean superficial femoral plaque area has also been shown to be significantly associated with poorer 6-minute walk time and slower walking velocity[12] in a separate study of 454 participants with PAD. Even after adjustment for the ABI, the associations of presence and characteristics of superficial femoral plaques with poorer physical function remained significant in both of these studies.[12,13] The current study extends these findings to a population-based study and shows that superficial femoral artery IMT, as well as plaque presence and burden, are important determinants of physical functioning even among relatively healthy older adults with a normal-range ABI.

The inconsistencies in the strength of associations between superficial and common femoral atherosclerosis could be possibly because of larger plaques creating worse stenosis in the superficial femoral artery, which in turn could lead to a lower level of physical functioning. Or, any amount of obstruction in the superficial femoral artery may result in a greater effect on physical functioning compared with plaque presence or a similar plaque burden in the common femoral artery. Anatomically, the superficial femoral artery feeds into the popliteal artery, and the superficial femoral is one of the most common sites of lower extremity atherosclerosis.[31,32] Additionally, the common femoral artery supplies blood to the thigh muscles while the superficial femoral artery supplies blood to calf muscles. Thus, superficial femoral artery obstruction may have a greater impact on any early declines in physical functioning, particularly for the 4-m walk or chair

rises, which are tests likely more dependent upon the calf musculature. For the 4-m walk, among participants with a normal-range ABI, we did observe concordant results in magnitude and direction between the superficial and common femoral IMT, albeit with marginal statistical associations for the common femoral IMT.

Inflammation and coagulation play a significant role in the atherosclerotic process and have previously been associated with femoral artery atherosclerosis.[14–18] However, in our study, after adjustment for demographics, lifestyle factors, and comorbid conditions, none of the inflammatory or coagulation markers appeared to be mediators of the femoral artery atherosclerosis and physical function associations. This held for both the whole range of the ABI and in the normal ABI group. In this regard, IL-6 does appear to be consistently associated with subclinical lower extremity atherosclerosis in both population-based studies and clinical samples with more severe lower extremity atherosclerotic disease.[17,18] This is partially supported by the mediation findings in our study, with IL-6 showing the most significant mediation effects in minimally adjusted models. However, upon further adjustment, IL-6 no longer appeared to be a mediator, indicating that the inflammation burden associated with other risk factors such as hypertension, diabetes mellitus, ever smoking, and dyslipidemia also contributes to the pathways between lower extremity atherosclerosis and physical function. It may also be that inflammation and coagulation have the most significant impacts, and are at their highest circulating levels, resulting in the highest inflammatory burden, in the latter stages of lower extremity atherosclerotic disease. These effects may not have been detected in the current study because the San Diego Population Study comprises largely healthy older adults, with a smaller proportion of PAD cases than a clinical sample might include.

A low ABI, a major clinical diagnostic criterion for PAD for over 40 years, has been associated with worse functional performance and status[7,9] and declines in physical function over time[10] in population-based studies. Our findings suggest, however, that the ABI may be insensitive for detecting early-stage lower extremity atherosclerotic disease. By the time the ABI progresses towards and below 0.90, hemodynamically significant fixed stenotic lesions are usually present (ie, stenosis >50%).[11] Flanigan et al reported that femoral artery ultrasound showed significant improvements in sensitivity compared with the ABI in detecting the presence of lower extremity atherosclerosis.[33] Additionally, use of femoral artery atherosclerosis measures may aid in cardiovascular risk stratification, even in low-risk individuals.[34] Taken together, this suggests that the superficial femoral artery for atherosclerosis may be superior to the ABI for successful, early identification of individuals with lower extremity disease, when intervention efforts to prevent disease progression and functional decline might be most effective.

Our study has several strengths but also some limitations to note. The San Diego Population Study is a large multiethnic population-based study, specifically designed to investigate lower extremity PAD, with standardized clinic examinations and assay measurement. However, our study was cross-sectional in nature; thus we cannot draw definitive conclusions regarding associations of femoral artery atherosclerosis and declines in physical function over time, especially among participants with a normal-range ABI. The femoral artery IMT and plaque measurements were performed with standardized protocols and quality control measures by trained ultrasound technicians. Our predominantly healthy older adult population enabled investigation of how femoral artery atherosclerosis was related to physical functioning even in participants who have normal-range ABIs and who are likely in the earlier stages of the lower-extremity disease process. For some images and some arterial segments, clear visualization of the IMT and plaques was difficult. However, we addressed this by using the far (posterior) artery wall to limit noise and measurement error for the IMT. We also performed sensitivity analysis, modeling plaque presence and total number of plaques with categorization as definite versus probable/no plaque. We modeled SPS as a perfect score (12) versus less than a perfect score. However, the modeling of SPS in this manner was appropriate for a population such as the one studied here, which is predominantly healthy, and it also aided in clinically relevant interpretation of the results. Also, one of our main aims was to identify early changes in physical function that may result from subclinical lower extremity atherosclerosis in participants with a normal-range ABI.

In a population-based multiethnic study of older adults, a greater burden of femoral artery atherosclerosis was associated with a lower overall SPS, and less favorable performance on its components, even among participants with a normal-range ABI. Significant associations were primarily for the superficial femoral artery, which may play a larger role than the common femoral artery in reduced physical functioning. Our study indicates that in early-stage atherosclerosis, femoral artery changes may detect abnormalities leading to poorer physical performance earlier in the course of PAD (ie, subclinical PAD) than those required, which result in a low ABI (≤0.90), typically considered PAD. While it may be prohibitive to screen all patients with a normal ABI for femoral artery atherosclerosis, it could be very beneficial for early detection in those who have other comorbidities such as type 2 diabetes mellitus or a family history of PAD, and a normal ABI. Indeed, family history of PAD is strongly associated with PAD.[35]

Findings also suggest that use of femoral artery atherosclerosis measures may be especially effective and beneficial in individuals with a normal-range ABI who are likely

asymptomatic, when detection can lead to earlier intervention to prevent functional declines and improve quality of life. Early interventions could range from lifestyle, such as an exercise program, to pharmacologic, such as initiation or intensification of statins. However, additional follow-up studies are first needed to confirm associations of femoral artery atherosclerosis with declines in physical function over time among those with a normal-range ABI.

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Disclosures

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