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Superficial Femoral Artery Plaque and Functional Performance in Peripheral Arterial Disease

Walking and Leg Circulation Study (WALCS III)

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OBJECTIVES We studied associations of magnetic resonance imaging measurements of plaque area and relative percent lumen reduction in the proximal superficial femoral artery with functional performance among participants with peripheral arterial disease.

BACKGROUND The clinical significance of directly imaged plaque characteristics in lower extremity arteries is not well established.

METHODS A total of 454 participants with an ankle brachial index <1.00 underwent magnetic resonance cross-sectional imaging of the proximal superficial femoral artery and completed a 6-min walk test, measurement of 4-m walking velocity at usual and fastest pace, and measurement of physical activity with a vertical accelerometer.

RESULTS Adjusting for age, sex, race, body mass index, smoking, statin use, comorbidities, and other covariates, higher mean plaque area (1st quintile [least plaque]: 394 m, 2nd quintile: 360 m, 3rd quintile: 359 m, 4th quintile: 329 m, 5th quintile [greatest plaque]: 311 m; p trend <0.001) and smaller mean percent lumen area (1st quintile [greatest plaque]: 319 m, 2nd quintile: 330 m, 3rd quintile: 364 m, 4th quintile: 350 m, 5th quintile: 390 m; p trend <0.001) were associated with shorter distance achieved in the 6-min walk test. Greater mean plaque area was also associated with slower usual-paced walking velocity (p trend = 0.006) and slower fastest-paced 4-m walking velocity (p trend = 0.003). Associations of mean plaque area and mean lumen area with 6-min walk distance remained statistically significant even after additional adjustment for the ankle brachial index and leg symptoms.

CONCLUSIONS Among participants with peripheral arterial disease, greater plaque burden and smaller lumen area in the proximal superficial femoral artery are associated independently with poorer functional performance, even after adjusting for the ankle brachial index and leg symptoms. (J Am Coll Cardiol Img 2011;4:730–9) © 2011 by the American College of Cardiology Foundation

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High-resolution magnetic resonance imaging (MRI) has emerged as a promising modality for direct atherosclerotic plaque imaging (1,2). However, little is known about associations of MRI-measured plaque area or lumen area with functional impairment in peripheral arterial disease (PAD). We used MRI to directly image cross sections of the superficial femoral artery (SFA) (Fig. 1). We studied associations of plaque area and percent lumen area in the SFA with functional impairment in PAD. We hypothesized that greater plaque area and smaller percent lumen area in the SFA would be associated with greater functional impairment, independently of age, comorbidities, and other potential confounders. We also hypothesized that significant associations of more adverse plaque characteristics with greater functional impairment would be eliminated after additional adjustment for the ankle brachial index (ABI).

METHODS

Subjects. Participants were identified from among consecutive PAD patients in the noninvasive vascular laboratories at Northwestern Memorial Hospital and 3 other Chicago-area medical centers. Participants were also identified from among lists of consecutive patients with a diagnosis of PAD in the vascular surgery, cardiology, endocrinology, general medicine, and geriatric practices at Northwestern Medical Faculty Foundation and in the vascular surgery practice at the Jesse Brown VA Medical Center. A small number of participants were identified from among men and women age 70 years and older in Northwestern's largest general internal medicine practice who were screened with the ABI and found to have an ABI <1.00 (Fig. 2). To maximize comparability with participants with previously established PAD, a minimum age of 70 years was required for participants identified in general medicine. The protocol was approved by the Institutional Review Boards of Northwestern University Feinberg School of Medicine and all participating sites. Participants gave written informed consent.

Inclusion criteria. The inclusion criterion was an ABI <1.00. This inclusion criterion was selected because truly normal ABI values are 1.10 to 1.40 (3–5) and because including participants with ABI <1.00 ensured a broad range of severity of lower extremity atherosclerosis. Presence of intermittent claudication was not an inclusion criterion.

Exclusion criteria. Potential participants with dementia and those with a Mini-Mental Status Examination score <23 (6) were excluded. Nursing home residents, wheelchair-bound patients, and patients with foot or leg amputations were excluded because of their severely impaired functioning. Non–English-speaking patients were excluded because investigators were not fluent in non-English languages. We excluded potential participants who required oxygen therapy, had contraindications to MRI testing, stopped the 6-min walk test due to shortness of breath, had recent major surgery, or had severe knee osteoarthritis. Severe arthritis was defined based on the presence of radiograph-measured osteoarthritis Kellgren-Lawrence score of 4 among participants who reported pain in or around

ABBREVIATIONS AND ACRONYMS

ABI = ankle brachial index
BMI = body mass index
MRI = magnetic resonance imaging
PAD = peripheral arterial disease
SFA = superficial femoral artery

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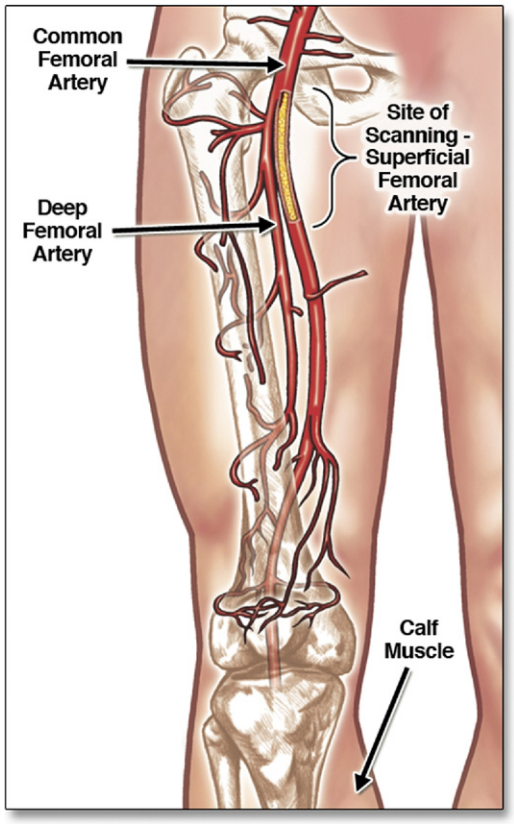

Figure 1. Location of SFA Imaging

Twelve 2.5-mm cross-sectional images were obtained from the proximal superficial femoral artery (SFA). The bifurcation of the common femoral artery was used as a landmark to define the start of the SFA. Figure illustration by Craig Skaggs.

their knee(s) on most days (7). All participants who reported pain in or around their knees on most days underwent a knee radiograph. Potential participants with bilateral superficial femoral artery stents were excluded, because the stents interfered with plaque imaging. Individuals with aortoiliac disease and those taking cilostazol were not excluded.

Ankle brachial index measurement. After participants rested supine for 5 min, a handheld Doppler probe (Nicolet Vascular Pocket Dop II, Golden, Colorado) was used to measure systolic pressures in this order: right brachial, dorsalis pedis, and posterior tibial arteries and left dorsalis pedis, posterior tibial, and brachial arteries. Pressures were repeated in reverse order. The ABI was calculated in each leg by dividing average pressures in each leg by the average of the 4 brachial pressures (8). Average brachial pressures in the arm with highest pressure were used when 1 brachial pressure was higher than the opposite brachial pressure in both measurement sets, and when the 2 brachial pressures differed by 10 mm Hg or more in at least 1 measurement set, because in such cases, subclavian stenosis was possible (9). Data from undetectable or incompressible dorsalis pedis and posterior tibial arteries were excluded from the ABI calculation. However, none of the participants had both undetectable dorsalis pedis and posterior tibial pressures in 1 leg, and no potential participants were excluded because of undetectable dorsalis pedis or posterior tibial pressures. Limbs with noncompressible vessels in both the dorsalis pedis and posterior tibial vessels were excluded from analyses.

Magnetic resonance imaging. We imaged the SFA because it is the most common site of lower extremity atherosclerosis (10,11) and because it supplies the calf muscle, which is typically symptomatic in patients with PAD. The leg with lowest ABI was imaged. However, if the leg with the lowest ABI had an SFA stent, the opposite leg was imaged. MRI data were obtained with a 1.5-T (Siemens, Malvern, Pennsylvania) platform using 4-element phased-array surface coils. We imaged the proximal region of the SFA because its superficial location was more amenable to high quality images than the distal SFA was. The bifurcation of the common femoral artery served as the reference point. Twelve consecutive 2.5-mm cross-sectional images were obtained, moving distally from the most proximal point of the SFA, using 2-dimensional bright blood time-of-flight and proton-density weighted images. Fat suppression was applied in black-blood sequences to improve image quality. This method has excellent test–retest reliability (12).

CASCADE software (Cascade Software Corporation, Seattle, Washington) was used by 2 physician-reviewers to trace the outer boundary and the lumen of each cross-sectional image of the SFA. CASCADE software quantified the plaque area based on the tracings. Plaque measurements were normalized for artery size (13). Specifically, for each participant, the measured mean and maximum plaque area were divided by the median of the outer wall area. To normalize lumen area measures, the mean and minimum lumen area were dividing by the outer wall area at each site. This normalization allowed us to take into account the fact that a given plaque size may have a different impact on study outcomes, depending on the size of the artery. Each reported plaque measure is normalized using these methods.

Images for each participant were assigned to a primary reviewer, and arterial tracings were re-

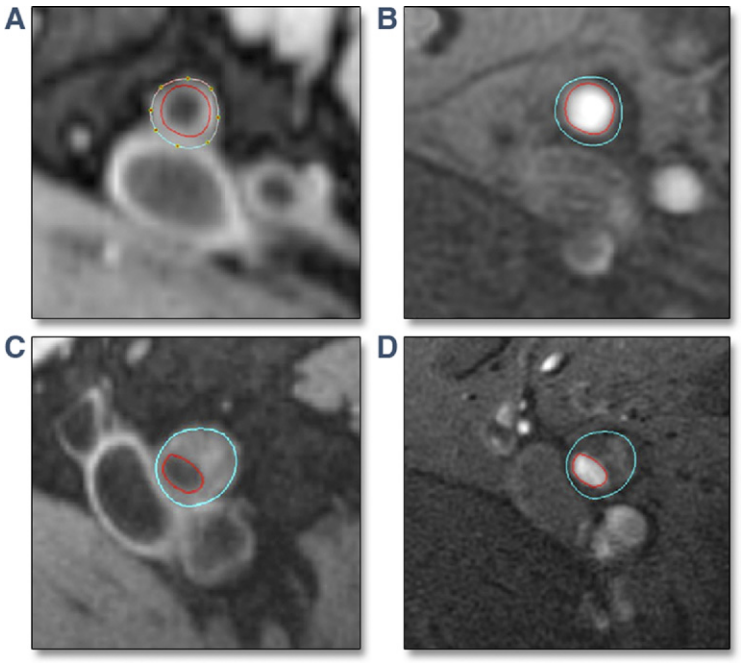

Figure 2. Representative Images of 2 Participants With Mild and Severe PAD

Images from a participant with minimal plaque **(A,B)** and from a participant with substantial plaque **(C,D).** Proton-weighted magnetic resonance images **(A,C)** (repetition time/echo time [TR/TE] = 2,160 ms/8 ms) and time of flight images **(B,D)** (TR/TE = 38 ms/8.7 ms) were used to define the outer **(blue contour)** and inner lumen boundaries **(red contour)**, respectively. PAD = peripheral arterial disease.

viewed by the second reviewer to ensure accuracy. In addition, independent readings by the 2 reviewers of the same artery were compared. The coefficient of variation percent values for these test inter-rater reliability assessments were 2.11 for mean plaque area, 4.24 for maximum plaque area, 1.77 for mean percent lumen reduction, and 1.77 for maximum percent lumen reduction.

A 6% subsample of participants returned on a second day for test–retest reliability assessment of MRI measurements. The coefficient of variation percent values for these test–retest reliability assessments were 5.8 for mean plaque area, 8.9 for maximum plaque area, 7.9 for mean percent lumen area, and 12.9 for minimum percent lumen area.

Functional Measures

Six-minute walk. Participants walk up and down a 100-foot hallway for 6 min with instructions to cover as much distance as possible (14,15). The distance walked at the end of 6 min was recorded. The intraclass correlation coefficient for test–retest reliability of the 6-min walk was 0.90 ($p < 0.001$) among 155 PAD participants in our laboratory who completed 2 tests 1 to 2 weeks apart (15).

Four-meter walking velocity. Walking velocity was measured with a 4-m walk performed at "usual" and "fastest" paces, based on previous study (14). For the usual-paced walk, participants were advised to walk at a normal pace, as if they were "walking down the street to go to the store." For the fast-paced walk, participants were advised to walk at their fastest speed. Each walk was performed twice. The faster walk in each pair was used in analyses (14).

Physical activity measurement. We used a vertical accelerometer (Caltrac, Muscle Dynamics Fitness Network Inc., Torrance, California) to measure physical activity continuously over 7 days using previously described methods (16,17). The accelerometer was programmed identically for all participants, allowing us to compare physical activity levels between participants, irrespective of individual variation in age, weight, height, and sex (16,17). Programmed in this way, the accelerometers measured "activity units."

Comorbidities. Algorithms developed for the Women's Health and Aging Study and the Cardiovascular Health Study were used to document comorbidities (18). These algorithms combine data from patient report, physical examination, medical record review, medications, laboratory values, and a primary care physician questionnaire (18). Comorbidities assessed were angina

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pectoris, diabetes mellitus, myocardial infarction, stroke, heart failure, pulmonary disease, cancer, spinal stenosis, and disk disease. Criteria from the American College of Rheumatology were used to diagnose knee and hip osteoarthritis (9,19).

Leg symptoms. Leg symptoms were classified using the San Diego claudication questionnaire (20). Intermittent claudication was defined as exertional calf pain that does not begin at rest, causes the participant to stop walking, and resolves within 10 min of rest. Participants without claudication were either asymptomatic (i.e., no exertional leg symptoms) or had exertional leg symptoms not consistent with claudication.

Other measures. Height and weight were measured at the study visit. Body mass index (BMI) was calculated as weight/height (kg/m^2). Cigarette smoking history was measured with self-report. Participants brought their medication bottles or a list of medications to their study visit. Medication names were recorded. The study principal investigator (M.M.M.) identified which participants were taking statin medications, but was blinded to participant characteristics.

Statistical analyses. Quintiles of mean and maximum plaque area and mean and minimum percent lumen area in the SFA, respectively, were defined. Differences in continuous and dichotomous variables were compared across these quintiles using analyses of variance and chi-square tests, respectively. Six-min walk performance, usual-paced and fastest-paced 4-m walking velocity, and physical activity levels were compared across quintiles of each plaque measure using analyses of covariance, adjusting for age, race, sex, smoking, BMI, statins, and comorbidities (model 1). These analyses were repeated with additional adjustment for the ABI (model 2). Model 2 was repeated adding adjustment for leg symptoms (model 3). For each plaque characteristic, pairwise comparisons were made between the lowest quintile and each of the remaining 4 quintiles.

With 454 PAD participants, this study had 80% power to detect a minimum partial correlation coefficient of 0.14 between 2 continuous measures, based on a 2-sided test at the significance level of 0.05. Analyses were performed using SAS statistical software (version 9.0, SAS Inc., Cary, North Carolina).

RESULTS

Figure 3 shows participation and exclusion rates among potential participants contacted for study. Of

Figure 3. Number of Excluded Individuals Among Those Contacted for Study Participation

ABI = ankle brachial index; MR = magnetic resonance; PAD = peripheral arterial disease.

3,391 men and women with PAD who received a recruitment letter, 1,161 did not respond. Of the remainder, 504 met 1 or more exclusion criteria, 954 refused participation, and 304 could not be scheduled or did not show for their study visit, leaving 468 PAD participants. An additional 4 PAD participants were identified from among patients in the general internal medicine practice who were screened with the ABI (Fig. 3). Of these 473 PAD participants, 16 had poor quality MR images and 3 were missing data for covariates, leaving 454 PAD participants.

Greater mean plaque area and smaller mean percent lumen area were each associated with older age, lower ABI values, higher prevalences of intermittent claudication, and lower prevalences of asymptomatic PAD (Table 1).

Adjusting for age, sex, race, smoking, BMI, statin use, and comorbidities, higher mean plaque area was associated with shorter distance achieved in the 6-min walk (p trend <0.001), slower usual-paced walking velocity (p trend = 0.006), and slower fastest-paced walking velocity (p trend = 0.002) (Table 2, model 1). After additional adjustment for ABI, these associations were attenuated but remained statistically significant (Table 2, model 2). After additional adjustment for leg symptoms, only associations of greater plaque area with shorter 6-min walk distance and slower rapid-paced 4-m walking velocity remained statistically significant (Table 2, model 3).

Adjusting for age, sex, race, smoking, BMI, statin use, and comorbidities, higher maximum plaque area was associated with shorter distance achieved in the 6-min walk (p trend <0.001), slower usual-paced walking velocity (p trend = 0.001), and slower fastest-paced walking velocity (p trend = 0.023) (Table 2, model 1). Associations of greater maximal plaque area with shorter 6-min walk distance and slower usual-paced 4-m walking velocity remained statistically

Table 1. Associations of Baseline Characteristics With Plaque Area and Percent Lumen Reduction in Participants With PAD

	Normalized Mean Vessel Plaque Area					
	Quintile 1 (0.38–0.56) (n = 90)	**Quintile 2 (0.56–0.62) (n = 91)**	**Quintile 3 (0.62–0.68) (n = 91)**	**Quintile 4 (0.68–0.81) (n = 91)**	**Quintile 5 (0.81–1.44) (n = 91)**	**Trend p Value**
Age, yrs	65.2 ± 11.0	69.6 ± 10.2	71.5 ± 9.9	71.2 ± 9.5	69.0 ± 9.0	0.040
Male	62.22	65.9	65.9	67.0	67.0	0.805
Black race	36.7	29.7	29.7	28.6	40.7	0.839
Ankle brachial index	0.76 ± 0.15	0.70 ± 0.17	0.71 ± 0.16	0.61 ± 0.15	0.56 ± 0.17	<0.001
Body mass index, kg/m^2	30.7 ± 6.8	29.3 ± 5.3	28.9 ± 5.6	28.7 ± 6.7	28.8 ± 5.3	0.049
Current smoking	23.3	26.4	26.4	20.9	25.3	0.604
Diabetes mellitus	38.9	50.6	33.0	36.3	34.1	0.171
Intermittent claudication	17.8	16.5	20.9	25.3	36.3	0.003
Asymptomatic	23.3	33.0	24.2	14.3	6.6	<0.001
Leg symptoms other than intermittent claudication	58.9	50.5	54.9	60.4	57.1	0.608
	Mean Percent Lumen Area					
	Quintile 1 (0.00–0.22) (n = 90)	**Quintile 2 (0.22–0.33) (n = 91)**	**Quintile 3 (0.33–0.38) (n = 91)**	**Quintile 4 (0.38–0.44) (n = 91)**	**Quintile 5 (0.44–0.60) (n = 91)**	**Trend p Value**
Age, yrs	69.3 ± 9.0	71.6 ± 9.9	71.6 ± 9.3	69.1 ± 10.3	64.9 ± 10.8	0.008
Male	66.7	63.7	73.6	61.5	62.6	0.916
Black race	42.2	28.6	24.2	36.3	34.1	0.343
Ankle brachial index	0.55 ± 0.16	0.63 ± 0.15	0.70 ± 0.17	0.71 ± 0.17	0.76 ± 0.15	<0.001
Body mass index, kg/m^2	28.9 ± 5.4	28.7 ± 6.6	28.5 ± 5.6	29.7 ± 5.6	30.5 ± 6.6	0.057
Current smoking	26.7	17.6	25.3	29.7	23.1	0.980
Diabetes mellitus	36.7	33.0	37.4	46.2	39.6	0.357
Intermittent claudication	38.9	25.3	22.0	13.2	17.6	0.001
Asymptomatic	8.9	14.3	19.8	37.4	20.9	0.001
Leg symptoms other than intermittent claudication	52.2	60.4	58.2	49.5	61.5	0.860

Values are mean ± SD or %.
PAD = peripheral arterial disease.

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Table 2. Associations of Plaque Characteristics With Functional Performance in Men and Women With PAD

		Normalized Mean Plaque Area					
		Quintile 1 (0.38–0.56) (n = 90)	**Quintile 2 (0.56–0.62) (n = 91)**	**Quintile 3 (0.62–0.68) (n = 91)**	**Quintile 4 (0.68–0.81) (n = 91)**	**Quintile 5 (0.81–1.44) (n = 91)**	**Trend p Value**
6-min walk, m	Model 1	394.4*	360.3†	359.4†	328.9	311.2	<.0001
	Model 2	382.5†	355.7	352.4	336.5	326.4	0.001
	Model 3	387.0†	361.5	360.0	350.5	338.3	0.004
Usual-paced 4-m walking velocity, m/s	Model 1	0.92†	0.87	0.89	0.86	0.84	0.006
	Model 2	0.92‡	0.86	0.89	0.86	0.85	0.047
	Model 3	0.92	0.87	0.90	0.88	0.87	0.092
Rapid-paced 4-m walking velocity, m/s	Model 1	1.29†	1.22	1.21	1.17	1.17	0.002
	Model 2	1.28‡	1.22	1.21	1.18	1.18	0.029
	Model 3	1.29‡	1.23	1.22	1.20	1.20	0.030
Physical activity, activity units	Model 1	811	827	749	683	733	0.087
	Model 2	804	825	746	687	743	0.179
	Model 3	817	845	770	725	782	0.360
		Normalized Maximum Plaque Area					
		Quintile 1 (0.44–0.70) (n = 90)	**Quintile 2 (0.70–0.78) (n = 91)**	**Quintile 3 (0.78–0.88) (n = 91)**	**Quintile 4 (0.88–1.05) (n = 91)**	**Quintile 5 (1.05–4.57) (n = 91)**	**Trend p Value**
6-min walk, m	Model 1	389*	373†	341	331	320	<.0001
	Model 2	376‡	367‡	341	336	334	0.008
	Model 3	377	375	350	350	347	0.032
Usual-paced 4-m walking velocity, m/s	Model 1	0.91†	0.88	0.90	0.86	0.84	0.001
	Model 2	0.90‡	0.88	0.90	0.86	0.85	0.007
	Model 3	0.91	0.89	0.90	0.88	0.86	0.017
Rapid-paced 4-m walking velocity, m/s	Model 1	1.27‡	1.24	1.21	1.16	1.17	0.023
	Model 2	1.26	1.23	1.21	1.17	1.19	0.118
	Model 3	1.27	1.24	1.23	1.19	1.20	0.158
Physical activity, activity units	Model 1	869‡	749	750	737	704	0.195
	Model 2	863‡	747	750	739	711	0.323
	Model 3	860	774	775	779	750	0.655
		Mean Percent Lumen Area					
		Quintile 1 (0.00–0.22) (n = 90)	**Quintile 2 (0.22–0.32) (n = 91)**	**Quintile 3 (0.32–0.38) (n = 91)**	**Quintile 4 (0.38–0.44) (n = 91)**	**Quintile 5 (0.44–0.60) (n = 91)**	**Trend p Value**
6-min walk, m	Model 1	319*	330*	364	350‡	390	<.0001
	Model 2	338‡	336‡	358	344‡	377	0.053
	Model 3	349‡	349‡	366	237	228	0.110
Usual-paced 4-m walking velocity, m/s	Model 1	0.85‡	0.87	0.89	0.86‡	0.91	0.047
	Model 2	0.87	0.87	0.89	0.85	0.90	0.283
	Model 3	0.88	0.89	0.89	0.87	0.91	0.426
Rapid-paced 4-m walking velocity, m/s	Model 1	1.17†	1.17†	1.22	1.20‡	1.28	0.006
	Model 2	1.19	1.18‡	1.22	1.20	1.27	0.069
	Model 3	1.20	1.20	1.23	1.22	1.29	0.065
Physical activity, activity units	Model 1	731	698	773	803	803	0.135
	Model 2	743	701	769	800	796	0.277
	Model 3	778	738	788	829	813	0.448

(Continued on next page)

Table 2. Continued

		Minimum Percent Lumen Area					
		Quintile 1 (0.00–0.08) (n = 90)	Quintile 2 (0.08–0.22) (n = 91)	Quintile 3 (0.22–0.29) (n = 91)	Quintile 4 (0.29–0.36) (n = 91)	Quintile 5 (0.36–0.55) (n = 91)	Trend p Value
6-min walk, m	Model 1	314*	333†	359	361	386	<.0001
	Model 2	329†	341	356	353	374	0.002
	Model 3	339‡	355	366	358	380	0.007
Usual-paced 4-m walking velocity, m/s	Model 1	0.84†	0.88	0.87	0.88	0.91	0.005
	Model 2	0.85‡	0.89	0.87	0.87	0.90	0.044
	Model 3	0.86	0.91	0.88	0.88	0.91	0.090
Rapid-paced 4-m walking velocity, m/s	Model 1	1.17‡	1.20	1.17‡	1.26	1.26	0.002
	Model 2	1.19	1.21	1.17‡	1.25	1.25	0.032
	Model 3	1.20	1.23	1.19	1.26	1.26	0.033
Physical activity, activity units	Model 1	725	757	701	799	827	0.041
	Model 2	736	762	699	793	819	0.092
	Model 3	771	800	728	808	839	0.217

Physical activity was measured over 7 days with a vertical accelerometer. Model 1 adjusts for age, sex, race, smoking, body mass index, statins, and comorbidities (angina, diabetes mellitus, myocardial infarction, stroke, heart failure, pulmonary disease, cancer, spinal stenosis, and disk disease). Model 2 adjusts for covariates in model 1 and the ankle brachial index. Model 3 adjusts for covariates in model 2 and leg symptoms. The p trend tests the degree to which associations across the plaque quintiles are linear. *$p < 0.001$; †$p < 0.01$; ‡$p < 0.05$.

significant after additional adjustment for the ABI (Table 2, model 2) and after additional adjustment for leg symptoms (Table 2, model 3).

Adjusting for age, sex, race, smoking, BMI, statin use, and comorbidities, lower mean percent lumen area was associated with shorter distance achieved in the 6-min walk (p trend <0.001), slower usual-paced walking velocity (p trend = 0.047), and slower fastest-paced walking velocity (p trend = 0.006) (Table 2, model 1). However, these associations were no longer significant after additional adjustment for the ABI.

Adjusting for age, sex, race, smoking, BMI, statin use, and comorbidities, smaller minimum percent lumen area was associated with shorter distance achieved in the 6-min walk (p trend <0.001), slower usual-paced walking velocity (p trend = 0.005), slower fastest-paced walking velocity (p trend = 0.002), and lower physical activity (p trend = 0.041) (Table 2, model 1). After additional adjustment for ABI, these associations remained statistically significant for the 6-min walk, usual-paced 4-m walking velocity, and fast-paced 4-m walking velocity (Table 2, model 2). After additional adjustment for leg symptoms, only associations of minimum percent lumen area with 6-min walk and rapid-paced 4-m walking velocity remained statistically significant (Table 2, model 3).

DISCUSSION

Among 454 PAD participants, our findings demonstrate, for the first time, that greater mean and maximum plaque area and smaller percent minimum lumen area in the proximal SFA are associated significantly and independently with poorer functional performance, even after adjusting for the ABI. Prior work by Anderson et al. (13) demonstrated that greater plaque area was associated with poorer 6-min walk performance ($r = -0.30$) and poorer maximum treadmill walking distance ($r = -0.32$) in 85 participants with PAD. However, these associations were not adjusted for confounders such as age, comorbidities, or the ABI (13). Identifying characteristics associated with the degree of functional impairment in PAD is important because these associations may provide clues to interventions that may improve functional performance in PAD.

Although participants with aorto-iliac (inflow) disease were included in the study, our results still demonstrated that plaque area and lumen area in the proximal superficial femoral artery were associated significantly with the degree of functional impairment in PAD. Our results suggest that plaque burden in the proximal superficial femoral artery may be a sensitive measure of lower extremity atherosclerotic disease burden, which in turn may be related to functional performance.

Associations of mean and maximum plaque area and minimum percent lumen area in the proximal SFA with some measures of functional performance remained statistically significant, even after adjustment for the ABI. This finding indicates that some associations of greater plaque area and smaller percent lumen area with greater functional perfor-

mance were independent of the ABI. The ABI is influenced by medial arterial calcinosis and does not change substantially over time, even as lower extremity perfusion deteriorates (21). Our findings suggest that mean and maximum plaque area and minimum percent lumen reduction may be better measures of the imbalance between oxygen supply and demand during walking than the resting ABI. It is also important to point out that some associations of plaque measures with functional impairment were further attenuated after additional adjustment for leg symptoms.

Glagov et al. (22) described the phenomenon of expansive remodeling, in which atherosclerotic plaque expands outwardly from the vessel wall, possibly in an attempt to maintain arterial lumen size as atherosclerosis develops. In our analyses, mean and maximum plaque area were more consistently associated significantly with impaired functional performance than mean percent lumen area. Our results suggest that for patients with PAD, outward plaque growth may not be protective against detrimental associations of lower extremity atherosclerotic plaque with impaired functional performance. However, expansive remodeling is most protective in arteries with lesser percent lumen reduction and may be less applicable to people with established or more severe PAD (22).

Study limitations. First, our findings may not be generalizable to PAD patients who did not meet our inclusion criteria, including potential participants with contraindications to MRI testing. Only 8 participants had an ABI <0.30. Thus, are findings are not generalizable to participants with critical limb ischemia. Second, we imaged the proximal superficial femoral artery because it is most amenable to MR imaging. The degree to which plaque area and percent lumen area in the proximal superficial femoral artery represent the degree of plaque area or percent lumen reduction in other sections of the SFA is unknown. Third, our methods did not allow us to separate calcification from other aspects of measured atherosclerotic plaque. Associations of plaque area with functional performance may have differed if our plaque area measurements excluded calcification. Fourth, we did not collect data in all participants on maximal stenosis of lower extremity atherosclerosis in each limb. Thus, our data could not be adjusted for this information.

CONCLUSIONS

This study demonstrates that greater plaque area and smaller plaque lumen are associated with greater functional impairment in participants with PAD. Our results should not be interpreted as a recommendation for additional or alternative diagnostic testing as compared with current clinical practice in patients with PAD. Further study is needed to determine whether plaque area and percent lumen reduction in the proximal SFA are associated with the degree of decline in functional performance among participants with PAD. Further study is also needed to determine whether interventions that reverse plaque burden can improve functional performance in PAD.

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