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Associations Between Lower Extremity Ischemia, Upper and Lower Extremity Strength, and Functional Impairment with Peripheral Arterial Disease

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Abstract

Objectives—To identify associations between lower extremity ischemia and leg strength, leg power, and hand grip in persons with and without lower extremity peripheral arterial disease (PAD). To determine whether poorer strength may mediate poorer lower extremity performance in persons with lower arterial brachial index (ABI) levels.

Design—Cross-sectional.

Setting—Academic medical centers.

Participants—Four hundred twenty-four persons with PAD and 271 without PAD.

Measurements—Isometric knee extension and plantarflexion strength and handgrip strength were measured using a computer-linked strength chair. Knee extension power was measured using the Nottingham leg rig. ABI, 6-minute walk, and usual and fastest 4-m walking velocity were measured. Results were adjusted for potential confounders.

Results—Lower ABI values were associated with lower plantarflexion strength (P trend = .04) and lower knee extension power (P trend < .001). There were no significant associations between ABI and handgrip or knee extension isometric strength. Significant associations between ABI and

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measures of lower extremity performance were attenuated after additional adjustment for measures of strength.

Conclusion—These results are consistent with the hypothesis that lower extremity ischemia impairs strength specifically in distal lower extremity muscles. Associations between lower extremity ischemia and impaired lower extremity strength may mediate associations between lower ABI values and greater functional impairment.

Keywords

intermittent claudication; peripheral arterial disease; physical functioning; limb ischemia; limb strength

Persons with lower extremity peripheral arterial disease (PAD) have impaired lower extremity performance and higher rates of functional decline than persons without PAD.^{1–3} In persons with PAD, lower ankle brachial index (ABI) levels are associated with greater functional impairment and faster rates of functional decline, although mechanisms of functional impairment and decline in PAD are not fully understood. Understanding whether reduced leg strength helps explain associations between low ABI values and functional impairment is important to elucidate mechanisms of disability in PAD and help identify optimal treatments for PAD-associated functional impairment.

This study determined whether lower ABI levels are associated with poorer knee extension power and poorer isometric measures of plantarflexion, knee extension, and handgrip strength in 695 persons with and without PAD. It was hypothesized that lower ABI values would be associated with poorer performance on measures of lower extremity strength but would not be associated with poorer handgrip strength, because PAD affects the lower extremity but not the upper extremity arteries. This study also determined whether lower levels of leg strength in persons with PAD might explain associations between lower ABI values and impaired lower extremity functioning. Statistical modeling was used to determine whether poorer lower extremity strength mediated associations between lower ABI values and poorer lower extremity functioning in persons with lower ABI values.

Methods

Participant Identification

The institutional review boards at the Northwestern University Feinberg School of Medicine and Catholic Health Partners Hospitals approved the protocol. Participants gave informed consent. Participants included persons attending their fourth annual follow-up visit in the Walking and Leg Circulation Study (WALCS) and newly identified participants for the present study (WALCS II).^{3,4} In WALCS and WALCS II, PAD participants were identified consecutively from among patients diagnosed with PAD in three Chicago-area non-invasive vascular laboratories. Participants without PAD were identified from among patients with normal lower extremity arterial studies in the three vascular laboratories and from consecutive patients in a large general internal medicine practice at Northwestern with a normal ABI. Because participants in the original WALCS cohort were aged 59 and older at the time of this data collection, an inclusion criterion for newly identified participants was aged 59 and older.

Of 368 participants returning for their fourth annual follow-up visit for the WALCS, 323 (87.8%) underwent measurement of one or more strength or power measures and were included in the present analyses. An additional 402 participants with and without PAD were newly identified for WALCS II, and 372 (92.5%) of these underwent measurement of leg strength or power.

Exclusion Criteria

PAD was defined as an ABI less than 0.90.^{5–8} At the time of enrollment for the WALCS and WALCS II cohorts, the following exclusion criteria were applied. Patients with dementia, defined as a Mini-Mental State Examination score less than 18, were excluded because of their inability to answer questions accurately. Nursing home residents, wheelchair-bound patients, and patients with foot or leg amputations were excluded, because they have severely impaired functioning. Non-English-speaking patients were excluded, because investigators were not fluent in non-English languages. Potential participants with recent major surgery were also excluded.

Ankle Brachial Index Measurement

The ABI was measured using established methods.^{4–6} After participants rested for 5 minutes, a handheld Doppler probe (Nicolet Vascular Pocket Dop II, Golden, CO) was used to measure systolic pressures in the right brachial artery, right dorsalis pedis and posterior tibial arteries, left dorsalis pedis and posterior tibial arteries, and left brachial artery. Each pressure was measured twice. The ABI was calculated by dividing average pressures in each leg by the average of the four brachial pressures.⁶ Average brachial pressures in the arm with the highest pressure were used when one brachial pressure was higher than the opposite brachial pressure in both measurement sets and the two brachial pressures differed by 10 or more mmHg in at least one measurement set, because, in such cases, subclavian stenosis was possible.⁷ Lowest leg ABI was used in the analyses.

Isometric Strength Measures

Leg strength was measured in Newtons using a computer-linked strength chair (Good Strength Chair, Metitur Oy, Jyväskylä, Finland).⁸ Transducers were placed for measurement of handgrip, knee extension, and plantarflexion. Handgrip strength was included as a measure of upper extremity strength to determine whether lower ABI values are associated with impairment in measures of lower extremity and upper extremity strength. Data were collected electronically by computer over 6 seconds. Strength measurements using the Good Strength Chair have high test-retest reliability (Pearson product moment correlations = 0.88–0.96).⁸ Two trials were performed, and the maximum strength was used in analyses.⁸

Leg Power

Validated methods previously developed were used to measure knee extension power in watts.⁹ The power rig uses a flywheel that is accelerated by pushing a footplate until the leg is extended.⁹ Power is derived from the final velocity of the flywheel measured with an optoswitch attached to a microcomputer. Testing was stopped when at least five trials had been performed and the two highest measures were within 5% of each other. Up to nine trials were performed.⁹

Six-Minute Walk

The 6-minute walk test is a reliable, valid measure of walking endurance in persons with PAD.^{1–3,10} The interclass correlation coefficient for test-retest reliability of the 6-minute walk was 0.89 ($P < .001$) in 139 participants with PAD who completed the tests approximately 1 to 2 weeks apart. Participants walked up and down a 100-foot hallway for 6 minutes after instructions to cover as much distance as possible.^{1,3}

Four-Meter Walking Velocity

Walking velocity was measured using a 4-m walk performed at “usual” pace and at fastest pace. Each walk (usual and fastest pace) was performed twice. The faster of two walks was

used in the analyses.^{11,12} The interclass correlation coefficients for test-retest reliability were 0.83 ($P<.001$) and 0.88 ($P<.001$), respectively, in 148 participants with PAD who completed the tests approximately 1 to 2 weeks apart. Participants were allowed to use assistive devices for the 4-m walks and 6-minute walk tests.

Leg Symptoms

Leg symptoms were classified into one of five groups based on previous study as follows:^{1,2,13} (1) intermittent claudication; (2) leg pain on exertion and rest; (3) atypical exertional leg pain, carry on; (4) atypical exertional leg pain, stop; and (5) asymptomatic.

Comorbidities

Algorithms developed for the Women's Health and Aging Study were used to document comorbidities, combining data from patient report, physical examination, medical record review, medications, laboratory values, and a primary care physician questionnaire.¹⁴ Comorbidities were angina pectoris, diabetes mellitus, myocardial infarction, stroke, heart failure, pulmonary disease, cancer, spinal stenosis, and disk disease. American College of Rheumatology criteria were used to adjudicate knee and hip osteoarthritis.^{15,16}

Other Measures

Height and weight were measured at the study visit. Body mass index (BMI) was calculated as weight (kg)/(height (m))². Cigarette smoking history was based on self-report.

Statistical Analyses

Associations between ABI and the strength and power outcomes were evaluated using tests for trend, adjusting for age, sex, race, cigarette smoking, BMI, leg symptoms, recruitment cohort (original WALCS vs newly identified), and comorbidities. These analyses were repeated within the subset of participants with PAD. Associations between ABI categories and lower extremity functional performance were assessed using tests for trend, adjusting for age, sex, race, comorbidities, BMI, leg symptoms, recruitment cohort, and smoking. To determine whether poorer strength may mediate these associations, additional multiple linear regression analyses were repeated with adjustment for strength measures that were found to be significantly related to the ABI. The estimated regression coefficients of the continuous ABI in regression models with and without adjustment for strength measures were compared. The potential mediation effects of the strength measures were summarized according to the ratio of the two regression coefficients of ABI in models with and without the adjustments for strength measures. Analyses were performed using SAS Statistical Software version 9.0 (SAS Institute, Inc., Cary, NC).

Results

Table 1 shows characteristics of participants with and without PAD. Participants with PAD were older and included a higher proportion of men; current smokers; and persons with diabetes mellitus, angina pectoris, pulmonary disease, and a history of myocardial infarction than those without PAD. Participants without PAD had higher prevalences of knee arthritis and spinal stenosis.

Participants with PAD had lower plantarflexion strength (329.75 ± 172.23 N vs 379.31 ± 180.63 N, $P=.001$) and lower knee extension power (93.49 ± 52.73 W vs 117.17 ± 68.6 W, $P<.001$) than those without PAD. There were no significant differences in knee extension isometric strength (271.9 ± 110.9 vs 290.01 ± 118.33 , $P=.06$) or handgrip strength (271.6 ± 115.90 vs 276.7 ± 109.41 , $P=.59$) between persons with and without PAD, respectively.

WALCS II participants without strength measurement data were older (75.71 ± 8.71 vs 73.58 ± 8.16 , $P = .03$), included a higher prevalence of men (50.95% vs 36.00%, $P = .01$), and had higher prevalences of knee arthritis (25.33% vs 14.53%, $P = .01$) and spinal stenosis (40.00% vs 25.61%, $P = .008$) than those with strength measurements.

Figures 1 and 2 show associations between ABI and the strength measures in participants with and without PAD. Within the entire cohort, lower ABI values were associated with lower plantarflexion strength (P trend = .04) and lower knee extension power ($P < .001$), adjusting for age, sex, race, comorbidities, BMI, smoking, leg symptoms, and recruitment cohort. Adjusted associations between ABI and plantarflexion strength remained significant when analyses were repeated within the subset of participants with PAD (P trend = .005). Within the subset of participants with PAD, there were no significant associations between ABI and knee extension power, after adjusting for confounders (data not shown). No significant associations between ABI and knee extension strength or handgrip strength were observed (Figure 1).

To determine whether poorer lower extremity strength in persons with PAD may mediate associations between lower extremity ischemia and functional impairment, stepwise multivariable regression models were performed. As shown in Table 2, lower ABI values were associated with significantly slower usual walking speed, fastest walking speed, and 6-minute walk performance, adjusting for age, sex, race, comorbidities, BMI, smoking, leg symptoms, and recruitment cohort (Model 1). After additional adjustment for plantarflexion strength and leg power, the association between ABI and fast-pace 4-m walking velocity was no longer statistically significant (Model 2, Table 2), and the association between ABI and usual-pace 4-m walking velocity was attenuated (Model 2, Table 2). The association between ABI and 6-minute walk performance remained statistically significant after additional adjustment for leg power and plantarflexion strength. Based on the ratio of the regression coefficients of ABI before and after the additional adjustment for lower extremity strength, the magnitude of the associations between ABI and fast-pace 4-m walking velocity, usual-pace 4-m walking velocity, and 6-minute walk were 59.6% (95% confidence interval (CI) = 40–89%), 47.2% (95% CI = 27–75%), and 25.9% (95% CI = 17–36%) less, respectively, after additional adjustment for strength measures (Table 2, Models 1 and 2).

Discussion

This study demonstrated that lower extremity ischemia was associated with poorer plantarflexion strength and poorer knee extension power in 695 persons with and without PAD. In contrast, there were no significant associations between ABI and handgrip strength. The finding that there was no association between PAD and upper extremity strength suggests that greater global weakness in persons with PAD that affects upper and lower extremity strength is not likely to explain associations between PAD and poorer lower extremity strength.

Clinically meaningful changes in performance measures were defined in a previous study.¹⁷ Based on these established definitions, in the present study, differences in fast-pace 4-m walking velocity between participants in the highest and lowest ABI categories were consistent with a substantial meaningful difference before adjusting for leg strength and power, although this substantial meaningful difference became consistent with a small meaningful difference after additional adjustment for leg strength and power. Similarly, modest meaningful differences in usual-pace 4-m walking velocity between participants in the highest and lowest ABI groups were no longer clinically significant after additional adjustment for leg strength and power. These findings support the hypothesis that poorer lower extremity strength in persons with PAD may mediate associations between lower ABI values and greater impairment in lower extremity performance, although differences in 6-minute walk performance between

the highest and lowest ABI categories were consistent with a substantial meaningful difference before and after adjustment for leg strength measures.

A previous study of calf muscle biopsies demonstrated that type I muscle fiber area was significantly smaller in 93 patients with PAD undergoing surgical procedures than corresponding muscle fibers obtained at autopsy from 30 people without PAD.¹⁸ In persons with unilateral PAD, muscle biopsies have also established that type II muscle fibers are smaller in the leg with PAD than in the leg without PAD.^{18,19} Neuropathic changes and denervation have also been established in calf muscle biopsies of patients with PAD,^{19,20} and these pathophysiological findings are associated with poorer lower extremity strength in PAD,¹⁹ although prior studies of associations between PAD and lower extremity strength have demonstrated mixed results.^{21–23} One study of 31 participants with and 15 without PAD found that those with PAD had significantly lower isometric dorsiflexion strength than those without PAD,²² but there were no differences in hip flexion, hip extension, knee flexion, knee extension, or plantarflexion strength between participants with and without PAD. In contrast, a separate study of 245 persons without and 269 persons with PAD and no prior lower extremity revascularization demonstrated that lower ABI levels were associated with poorer hip extension, hip flexion, and knee flexion strength.²¹ Clinical trials of lower extremity resistance training in persons with PAD have also demonstrated mixed results.^{24,25} One study found significant increases in leg strength and pain-free treadmill walking distance in 20 persons with PAD randomized to 24 weeks of lower extremity resistance training. Muscle biopsies showed more type I muscle fibers and type II muscle fibers and greater capillary density in the strength-trained group than in controls,²⁴ although in a separate study of 29 men with claudication randomized to 12 weeks of treadmill walking exercise, lower extremity strength training, or control, treadmill walking performance improved most significantly in the treadmill-trained group, and the authors concluded that strength training was not beneficial for persons with PAD.²⁵ Thus, the association between lower extremity ischemia and strength in specific muscle groups is still unclear, and the degree to which poorer strength contributes to the causal pathway of lower extremity ischemia and impaired functional performance in persons with PAD is not well delineated.

To the authors' knowledge, no prior studies have demonstrated a significant association between lower ABI values and poorer plantarflexion strength in persons with and without PAD. The results of the current study may differ from those previously reported²² because of the substantially larger sample size in the WALCS II cohort. Plantarflexion weakness in persons with PAD is consistent with the fact that the superficial femoral artery, the most common site of atherosclerosis below the inguinal ligament,^{26,27} supplies blood to the calf muscle. In addition, to the authors' knowledge, no prior studies have assessed associations between ABI and upper and lower extremity strength. Findings reported here suggest that associations between PAD and impaired strength may be limited to the lower extremities, although because handgrip strength is one of many potential measures of upper extremity strength, additional study is needed.

This study has limitations. Findings may not be generalizable to individuals younger than 59 or to nursing home residents. Associations studied were cross-sectional and cannot be construed as causal.

Conclusion

Lower extremity ischemia is associated with poorer distal lower extremity strength but not poorer upper extremity strength, as measured according to handgrip strength. Data presented here are consistent with the hypothesis that PAD-related impairments in lower extremity strength may mediate associations between PAD and impaired lower extremity functioning,

although longitudinal studies are needed to further establish whether poorer lower extremity strength is in the causal pathway linking PAD with functional impairment and decline.

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Figure 1.

Associations between ankle brachial index and upper and lower extremity strength in persons with and without peripheral arterial disease (n = 596). Analyses were adjusted for age, sex, race, comorbidities, body mass index, smoking, leg symptoms, and recruitment cohort.

Figure 2.

Associations between ankle brachial index and lower extremity power in persons with and without peripheral arterial disease (n = 676). Analyses were adjusted for age, sex, race, comorbidities, body mass index, smoking, leg symptoms, and recruitment cohort.

Table 1
Characteristics of Men and Women Aged 59 and Older with and without Peripheral Arterial Disease (PAD)

Characteristic	No PAD (n=271)	PAD (n=424)	P-Value
Age, mean $\pm$ SD	71.39 $\pm$ 7.56	74.97 $\pm$ 8.24	<.001
Ankle brachial index, mean $\pm$ SD	1.09 $\pm$ 0.09	0.63 $\pm$ 0.15	<.001
Body mass index, kg/m ² , mean $\pm$ SD	29.15 $\pm$ 6.03	27.71 $\pm$ 4.91	<.001
Male, %	43.54	55.66	.002
African American, %	20.66	16.27	.14
Current smoker, %	5.20	15.80	<.001
Walking aid, %	8.30	12.20	.11
Comorbidities, %			
Angina pectoris	20.52	34.37	<.001
Myocardial infarction	15.50	26.00	.001
Diabetes mellitus	23.25	32.08	.01
Knee arthritis	19.19	11.56	.005
Hip arthritis	4.43	3.54	.55
Spinal stenosis	41.70	15.33	<.001
Disk disease	32.84	39.62	.07
Cancer	22.88	20.99	.56
Pulmonary disease	34.69	43.16	.03

SD = standard deviation.

Table 2
Mediating Effects of Lower Extremity Strength on Associations Between Ankle Brachial Index (ABI) and Functional Impairment in Persons with and without Peripheral Arterial Disease

Functional Performance Measure	ABI					P-Trend
	Adjusted Mean Value					
	<0.50	0.50 to <0.70	0.70 to <0.90	0.90 to <1.00	1.00 to <1.30	
Fast-paced 4-m walking velocity, m/s						
Model 1 *	1.17	1.24	1.19	1.24	1.29	.001
Model 2 †	1.21	1.25	1.20	1.25	1.27	.06
Usual-pace 4-m walking velocity, m/s						
Model 1 *	0.88	0.90	0.89	0.92	0.95	.001
Model 2 †	0.90	0.91	0.90	0.92	0.94	.02
6-minute walk, feet						
Model 1 *	1,060	1,194	1,230	1,342	1,417	<.001
Model 2 †	1,096	1,204	1,248	1,355	1,396	<.001

* Adjusted for age, sex, race, comorbidities, body mass index, leg symptoms, smoking, and recruitment cohort.

† Adjusted for age, sex, race, comorbidities, body mass index, leg symptoms, smoking, recruitment cohort, and plantarflexion and knee extension power.