Journal of the American College of Cardiology
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Published by Elsevier Inc.

Vol. 50, No. 9, 2007
ISSN 0735-1097/07/$32.00
doi:10.1016/j.jacc.2007.05.017

Elevated Levels of Inflammation, D-Dimer, and Homocysteine Are Associated With Adverse Calf Muscle Characteristics and Reduced Calf Strength in Peripheral Arterial Disease

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Objectives This study determined whether increased levels of inflammatory blood markers, D-dimer, and homocysteine were associated with smaller calf skeletal muscle area, increased calf muscle percent fat, reduced calf muscle density, and poorer calf strength in persons with lower extremity peripheral arterial disease (PAD).

Background Elevated levels of inflammatory markers and D-dimer are associated with greater functional impairment and functional decline in persons with PAD. Mechanisms of these associations are unknown.

Methods Participants were 423 persons with PAD. Calf muscle area, percent fat, and density were measured with computed tomography. Physical activity levels were measured objectively over 7 days with the Caltrac (Muscle Dynamics Fitness Network, Inc., Rocklin, California) vertical accelerometer. Isometric plantarflexion strength was measured. Analyses were adjusted for age, gender, race, comorbidities, the ankle-brachial index, and other potential confounders.

Results Higher levels of D-dimer ($p = 0.014$), C-reactive protein (CRP) ($p = 0.002$), interleukin (IL)-6 ($p < 0.001$), and soluble vascular cellular adhesion molecule (sVCAM)-1 ($p = 0.008$) were associated with smaller calf muscle area. Higher sVCAM-1 ($p = 0.004$) and IL-6 ($p = 0.017$) were associated with higher calf muscle percent fat. Higher D-dimer ($p < 0.001$), sVCAM-1 ($p < 0.001$), and homocysteine ($p = 0.014$) were associated with lower calf muscle density. These associations were generally unchanged after additional adjustment for physical activity. Higher sVCAM-1 ($p = 0.013$) was associated with lower calf strength.

Conclusions These data show, for the first time, that higher levels of inflammation, D-dimer, and homocysteine are associated with more adverse calf muscle characteristics in persons with PAD. These associations may contribute to previously established associations between elevated biomarkers and functional impairment and functional decline in PAD. (J Am Coll Cardiol 2007;50:897–905) © 2007 by the American College of Cardiology Foundation

Chronic inflammation has been proposed as a biologic mechanism underlying aging-related functional decline. An inflammatory state characterized by increased levels of inflammatory cytokines and markers may contribute to sarcopenia, an age-related reduction in muscle strength and mass (1–5). Persons with peripheral arterial disease (PAD) have increased levels of inflammatory blood markers and increased functional impairment compared with persons

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Manuscript received November 28, 2006; revised manuscript received April 2, 2007, accepted May 8, 2007.

Abbreviations and Acronyms

ABI = ankle-brachial index
BMI = body mass index
CRP = C-reactive protein
CT = computed tomography
ELISA = enzyme-linked immunosorbent assay
HDL = high-density lipoprotein
IL = interleukin
PAD = peripheral arterial disease
sICAM-1 = soluble intracellular adhesion molecule
sVCAM-1 = soluble vascular cellular adhesion molecule

without PAD (6–8). We previously reported (9) that increased levels of D-dimer and C-reactive protein (CRP) are associated with poorer lower extremity functional performance in persons with PAD, independent of confounders. Elevated levels of inflammation and D-dimer are associated with faster rates of functional decline in persons with PAD (10). Mechanisms of these associations are unclear. Therefore, we studied associations of elevated levels of inflammatory blood markers with calf skeletal muscle characteristics and leg strength in persons with PAD. D-dimer and homocysteine were also studied. We studied D-dimer because it is an end product of fibrinolysis and may promote the inflammatory cascade by activating neutrophils and monocytes, inducing secretion of inflammatory cytokines (including interleukin [IL]-6), and promoting hepatic synthesis of acute-phase proteins (11–14). We studied homocysteine because it may contribute to skeletal muscle weakness and atrophy by affecting the ability of cells to regenerate and respond to trophic stimuli (15,16). Calf muscle characteristics studied were calf muscle area, calf muscle percent fat, and calf muscle density. Calf muscle density is a measure of muscle fiber number per unit area and may be a measure of muscle quality. We hypothesized that higher levels of each blood marker would be associated with smaller muscle area, higher calf muscle percent fat, lower calf muscle density, and lower calf muscle strength in persons with PAD. To determine whether significant associations of blood markers with strength were specific to the calf muscle, we also studied associations between blood markers with grip strength.

Methods

Participant identification. The protocol was approved by the Institutional Review Boards of Northwestern University Feinberg School of Medicine and Catholic Health Partners Hospitals. Participants gave informed consent. Participants included persons with PAD attending their fourth annual follow-up visit in the WALCS (Walking and Leg Circulation Study) (8,17) and newly identified PAD participants for the present study (WALCS II). In both WALCS and WALCS II, PAD participants were identified consecutively from among patients diagnosed with PAD in 3 Chicago-area noninvasive vascular laboratories. Data were collected between November 2002 and May 2004. Because participants in the original WALCS cohort were age 59 and older at the time of this data collection, an inclusion criterion for newly identified participants was age 59 or older.

Of 238 PAD participants returning for their fourth annual follow-up visit for the WALCS, 214 underwent computed tomography (CT) scanning and were included in the present analyses. An additional 240 participants with PAD were newly identified for WALCS II and underwent CT scanning. Of these, 202 (85%) from WALCS and 221 (92%) of those newly identified underwent blood draw at their visit and were eligible for the present study.

Exclusion criteria. Peripheral arterial disease was defined as ankle-brachial index (ABI) <0.90 (17–20). Patients with recent major surgery were excluded. At the time of enrollment for both WALCS and WALCS II, the following exclusion criteria were applied. Patients with dementia 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 had severely impaired functioning. Non–English-speaking patients were excluded because investigators were not fluent in non-English languages.

ABI measurement. The ABI was measured using established methods (8,17–20). After participants rested supine for 5 min, a hand-held Doppler probe (Nicolet Vascular Pocket Dop II, Golden, Colorado) 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: in the order listed and then 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 (17,20). 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 the 2 brachial pressures differed by 10 or more mm Hg in at least 1 measurement set, because in such cases subclavian stenosis was possible (21). Lowest leg ABI was used in analyses.

Measuring calf muscle characteristics. Using a CT scanner (LightSpeed, General Electric Medical Systems, Waukesha, Wisconsin), we obtained a 2.5-mm cross-sectional image of the calves at 66.7% of the distance from the distal to the proximal tibia (22). BonAlyse software (BonAlyse Ltd., Jyvaskyla, Finland) was used to measure characteristics of muscle, as follows. The muscle outline was traced manually and excluded subcutaneous fat and bone. When measuring muscle area, the BonAlyse software quantifies voxels within a range corresponding to muscle density (9 to 271 mg/cm^3) and excludes voxels corresponding to fat density (−270 to 8 mg/cm^3). Intramuscular fat is quantified by summing voxels corresponding to fat within muscle tissue. Muscle density measures the amount of muscle per volume, within the range corresponding to muscle (9 to 271 mg/cm^3), and is a measure of muscle quality. Previous cadaver studies (23) demonstrate that these methods pro-