Journal of the American College of Cardiology
© 2012 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 59, No. 13, 2012
ISSN 0735-1097/$36.00
doi:10.1016/j.jacc.2011.12.019

Calf Muscle Characteristics, Strength Measures, and Mortality in Peripheral Arterial Disease

A Longitudinal Study

Mary M. McDermott, MD,*† Kiang Liu, PhD,† Lu Tian, ScD,‡ Jack M. Guralnik, PhD,§
Michael H. Criqui, MD, MPH,‖ Yihua Liao, MS,† Luigi Ferrucci, MD, PhD¶

Chicago, Illinois; Palo Alto and San Diego, California; and Baltimore and Bethesda, Maryland

Objectives This study analyzed whether lower calf muscle density and poorer upper and lower extremity strength are associated with higher mortality rates in men and women with peripheral arterial disease (PAD).

Background Men and women with lower extremity PAD have lower calf muscle density and reduced lower extremity strength compared with individuals without PAD.

Methods At baseline, participants underwent measurement of calf muscle density with computed tomography in addition to knee extension power and isometric knee extension, plantar flexion, and hand grip strength measures. Participants were followed up annually for up to 4 years. Results were adjusted for age, sex, race, body mass index, ankle-brachial index, smoking, physical activity, and comorbidities.

Results Among 434 PAD participants, 103 (24%) died during a mean follow-up of 47.6 months. Lower calf muscle density was associated with higher all-cause mortality (lowest density tertile hazard ratio [HR]: 1.80 [95% confidence interval (CI): 1.07 to 3.03], second tertile HR: 0.91 (95% CI: 0.51 to 1.62); highest density tertile HR: 1.00; p trend = 0.020) and higher cardiovascular disease mortality (lowest density tertile HR: 2.39 [95% CI: 0.90 to 6.30], second tertile HR: 0.85 [95% CI: 0.27 to 2.71]; highest density tertile HR: 1.00; p trend = 0.047). Poorer plantar flexion strength (p trend = 0.004), lower baseline leg power (p trend = 0.046), and poorer hand-grip (p trend = 0.005) were associated with higher all-cause mortality.

Conclusions These data demonstrate that lower calf muscle density and weaker plantar flexion strength, knee extension power, and hand grip were associated with increased mortality in these participants with PAD, independently of the ankle-brachial index and other confounders. (J Am Coll Cardiol 2012;59:1159–67) © 2012 by the American College of Cardiology Foundation

Lower extremity peripheral arterial disease (PAD) affects 8 million men and women in the United States (1). The prevalence is expected to increase as the population lives longer with chronic disease. Men and women with PAD have greater lower extremity functional impairment and faster functional decline than people without PAD (2,3). Lower extremity skeletal muscle, particularly calf muscle, is the end organ affected by obstructed lower extremity arteries in PAD. Consistent with this association, individuals with PAD have more adverse calf muscle characteristics and poorer lower extremity strength than people without PAD (4,5). Histopathologic data demonstrate that lower extremity ischemia is associated with calf muscle apoptosis, type II muscle fiber atrophy, and impaired mitochondrial function (5–7). An improved understanding of the prognostic significance of lower extremity muscle pathophysiological changes in PAD may help delineate mechanisms of adverse outcomes in PAD.

We studied associations of computed tomography (CT)-measured calf muscle density, calf muscle area, and calf

From the *Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, Illinois; †Department of Preventive Medicine, Northwestern University Feinberg School of Medicine, Chicago, Illinois; ‡Department of Health Research and Policy-Biostatistics, Stanford University, Palo Alto, California; §Department of Epidemiology & Public Health, University of Maryland School of Medicine, Baltimore, Maryland; ‖Division of Preventive Medicine, University of California at San Diego, San Diego, California; and the ¶Intramural Research Program, National Institute on Aging, Bethesda, Maryland. This study was supported by grants R01-HL58099, R01-HL64739, R01-HL071223, R01-HL076298, and R01-HL083064 from the National Heart, Lung, and Blood Institute and by grant RR-00048 from the National Center for Research Resources, National Institutes of Health. Supported in part by the Intramural Research Program, National Institute on Aging, National Institutes of Health. The authors have reported that they have no relationships relevant to the contents of this paper to disclose. Alan T. Hirsch, MD, served as Guest Editor for this paper.

Manuscript received July 22, 2011; revised manuscript received November 17, 2011, accepted December 14, 2011.

Abbreviations and Acronyms

ABI = ankle-brachial index

BMI = body mass index

CT = computed tomography

HR = hazard ratio

PAD = peripheral arterial disease

muscle percent fat with mortality rates in men and women with PAD. We hypothesized that lower calf muscle density, lower calf muscle area, and higher calf muscle percent fat would be associated with higher all-cause and cardiovascular disease mortality. We also studied associations of knee extension power, knee extension isometric strength, and plantar flexion isometric strength with mortality in people with PAD. We hypothesized that poorer knee extension power, knee extension strength, and plantar flexion strength would be associated with higher all-cause and cardiovascular disease mortality. To determine whether associations of poorer strength with higher mortality are systemic in people with PAD, we studied associations of hand grip isometric strength with mortality.

Methods

Study overview. The institutional review boards of Northwestern University and Catholic Health Partners Hospital approved the protocol. Participants provided written informed consent. Participants were part of the WALCS II (Walking and Leg Circulation Study II), a prospective, observational study designed to identify associations of calf skeletal muscle characteristics and leg strength with functional performance and functional decline in people with and without PAD (4,8,9). Participants underwent baseline measures and returned annually for follow-up. Participants were also followed up for the outcome of mortality.

Participant identification. PAD participants in WALCS II included 223 patients with PAD attending their fourth annual follow-up visit in the original WALCS (4,8) and 240 with PAD newly identified for WALCS II.

PAD participants were identified from among consecutive patients diagnosed with PAD in 3 Chicago-area noninvasive vascular laboratories (4,8,9). A small number of PAD participants were identified from among consecutive patients in a large general internal medicine practice who were found to have a low ankle-brachial index (ABI) at their study visit and were included among PAD participants (4,8). PAD was defined as an ABI <0.90 at the baseline visit for WALCS II (4,8). All participants were age ≥59 years at baseline.

Participation rates and exclusion criteria for the WALCS II cohort have been described previously (4,9). The following exclusion criteria were applied at the time of original study enrollment to participants in the original WALCS cohort and those newly identified. 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 the investigators were not fluent in non-English languages. Patients with recent major surgery were also excluded.

ABI measurement. A handheld Doppler probe (Nicolet Vascular Pocket- Dop II; Nicolet Biomedical Inc., Golden, Colorado) was used to obtain systolic pressures in the right and left brachial, dorsalis pedis, and posterior tibial arteries (2,4,8). Each pressure was measured twice. The ABI was calculated by dividing the mean of the dorsalis pedis and posterior tibial pressures in each leg by the mean of the 4 brachial pressures (2,4,8). Zero values for the dorsalis pedis and posterior tibial pulses were set to missing for the ABI calculation. Average brachial pressures in the arm with highest pressure were used when one brachial pressure was higher than the opposite brachial pressure in both measurement sets and the 2 brachial pressures differed by ≥10 mm Hg in at least 1 measurement set; this action was taken because in such cases, subclavian stenosis was possible (10). The lowest leg ABI was used in analyses.

Measuring calf skeletal muscle characteristics. We studied calf muscle characteristics because the superficial femoral artery is the most common site of lower extremity atherosclerosis (11,12) and calf musculature receives blood supply from the superficial femoral artery. Furthermore, the calf muscles are those that classically are symptomatic in patients with PAD (13). Using a CT scanner (LightSpeed, GE Medical Systems, Waukesha, Wisconsin), 2.5-mm cross-sectional images of the calves were obtained at 66.7% of the distance from the distal to the proximal tibia without contrast (4,9). Cross-sectional calf muscle images were analyzed by using BonAlyse (BonAlyse Oy, Jyväskylä, Finland), a software for processing CT images that identifies muscle tissue, fat, and bone (4,9). The muscle outline was traced manually, excluding subcutaneous fat and bone, by a study coordinator who was trained and certified in these measures before beginning analyses. When quantifying 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 tissue density within muscle tissue. Previous cadaver studies demonstrated that these methods provide an estimate of muscle cross-sectional area and fat content that are highly correlated with direct anatomic measures (14). Specifically, correlations between CT-measured skeletal muscle and lipid content with corresponding measures from cadavers were 0.97 and 0.96, respectively. Because larger individuals require greater muscle mass to support their larger frame, muscle area was adjusted for the square of individual tibia length (4,9). Muscle density is a measure of muscle quantity within a defined volume. Across the voxel range corresponding to muscle tissue (9 to 271 mg/cm^3), individuals have varying quantities of muscle per centimeter cubed (i.e., they range from 9 to 271). Mean muscle density was calculated per