Peripheral Arterial Disease Is Associated With Higher Rates of Hip Bone Loss and Increased Fracture Risk in Older Men

Tracie C. Collins, MD, MPH; Susan K. Ewing, MS; Susan J. Diem, MD, MPH; Brent C. Taylor, PhD; Eric S. Orwoll, MD; Steven R. Cummings, MD; Elsa S. Strotmeyer, PhD, MPH; Kristine E. Ensrud, MD, MPH; for the Osteoporotic Fractures in Men (MrOS) Study Group

Background—Peripheral arterial disease (PAD) and osteoporosis are chronic illnesses that increase in prevalence with aging and certain metabolic disorders. The association between PAD, rates of bone loss, and fracture risk in older men is uncertain.

Methods and Results—We sought to test the hypothesis that PAD is associated with higher rates of bone loss and increased fracture risk. We analyzed data from a prospective cohort study involving 6 US centers and 5781 men at least 65 years of age. We assessed ankle-brachial index and hip bone mineral density, followed up prospectively for changes in hip bone mineral density and fractures. PAD was defined as a baseline ankle-brachial index <0.9. Hip bone mineral density was measured with dual x-ray absorptiometry at baseline and again an average of 4.6 years later. Incident nonspine fractures were ascertained by self-report and confirmed with radiography reports during an average of 5.4 years of follow-up. At baseline, the prevalence of PAD was 6.2%. After adjustment for age, race, site, and baseline bone mineral density, the mean annualized rate of bone loss at the total hip was −0.66% per year (95% confidence interval −0.78 to −0.54) in men with PAD compared with −0.34% per year (95% confidence interval −0.36 to −0.31) in men without PAD (P<0.001). After further adjustment for multiple potential confounders, the difference was attenuated (−0.49% in men with PAD versus −0.35% in men without PAD) but remained significant (P=0.02). Findings were similar at hip subregions. Twelve percent of men with PAD and 7.9% of those without PAD experienced an incident nonspine fracture (hazard ratio adjusted for age, race, and site 1.47, 95% confidence interval 1.07 to 2.04); this association was not altered substantially by further adjustment for multiple confounders.

Conclusions—In community-dwelling older men, PAD was associated with higher rates of hip bone loss and increased risk of nonspine fractures. Further research should examine the biological mechanisms underlying the association between reduced limb blood flow and fractures. (Circulation. 2009;119:2305-2312.)

Key Words: peripheral arterial disease ■ bone loss ■ fractures

Fractures related to osteoporosis and peripheral arterial disease (PAD) are major causes of morbidity and mortality in older people.1,2 Evidence exists to support an association between atherosclerosis of peripheral vessels and osteoporosis. Laroche et al3 conducted a study of 25 patients with unilateral lower-limb PAD and reported that bone mineral density (BMD) at the femur, ankle, and foot was lower in the PAD-affected limb than in the unaffected limb. Similarly, Pennisi et al4 conducted a case-control study and found lower spine and hip BMD among 36 patients with either carotid or femoral atherosclerosis than among age- and gender-matched control subjects. In addition, previous large observational studies have provided evidence of an association between low BMD and either incident cardiovascular disease5 or subclinical atherosclerosis.6–8

Clinical Perspective on p 2312

However, most prior investigations that examined the association between PAD and bone health were cross-sectional analyses of patient populations selected on the basis of their risk for PAD and were focused primarily on women. Thus, findings may not be applicable to a longitudinal
assessment of unselected community-dwelling older men. Prospective studies are needed to accurately examine the association between PAD and subsequent rates of bone loss and fracture risk. To test the hypothesis that older men with PAD have increased rates of bone loss and higher fracture risk, we measured ankle-brachial index (ABI) and hip BMD in a cohort of community-dwelling men 65 years of age and older in the Osteoporotic Fractures in Older Men (MrOS) study and followed them prospectively for changes in BMD and fractures.

**Methods**

**Participants**

From March 2000 to April 2002, 5995 men at least 65 years old were recruited for participation in the baseline examination of the prospective MrOS study, a large observational study of the determinants of fracture risk in older men. Men were recruited from population-based listings in Birmingham, Ala; Minneapolis, Minn; the Monongahela Valley, Pa; Palo Alto, Calif; Portland, Ore; and San Diego, Calif. Of the 5995 men enrolled in MrOS, 5781 (96.4%) had ABI data at the baseline examination (Figure 1). Of the 214 men without ABI measurements, measurements were attempted but not completed on 116 men because of an inability to occlude or locate the tibial arteries, or for other reasons; 74 men refused to be measured; and 24 men met exclusion criteria (20 with open wounds or ulcerations, 3 who were unable to lie at a 45° angle, and 1 who had bilateral amputations). A total of 4409 (76% of active survivors) of the 5781 men with baseline ABI data attended a second clinic examination between March 2005 and April 2006. Of these, 4302 completed a technically adequate hip BMD measurement at both examinations and were included in the analyses investigating the association between PAD and rate of change in hip BMD. All 5781 men with baseline ABI measurements were included in the analyses examining the association between PAD and risk of incident fractures (Figure 1). The appropriate institutional review boards reviewed the study, and written informed consent was obtained from all study participants.

**Measurement of BMD**

BMD (g/cm²) of the total hip and its subregions (femoral neck; trochanter) was measured at the 2 examinations (mean 4.6 [0.3 SD] years between examinations) with fan-beam dual-energy x-ray absorptiometry (QDR 4500W, Hologic Inc, Bedford, Mass). Further details of the measurement method, densitometry quality control procedures, and precision of the measurements in the present study cohort have been published elsewhere. For the primary analysis, the rate of change in BMD was expressed as an annualized percentage of the difference between the follow-up BMD and initial BMD divided by the initial BMD.

**Ascertainment of Fractures**

We contacted participants by postcard or telephone every 4 months to ask whether they had sustained a fracture. We were able to complete 99% of these contacts in surviving men. Fractures were verified by physician adjudication of medical records and x-ray reports. Unconfirmed and pathological fractures were not considered in the analyses. All confirmed fractures that occurred and were adjudicated after the baseline examination and by August 1, 2007, were included in these analyses. Average follow-up was 5.4 (1.4 SD) years for nonspine fractures and 5.6 (1.2 SD) years for hip fractures.

**Peripheral Arterial Disease**

The diagnosis of PAD was based on the ABI, the ratio of the systolic pressure in the ankle to that in the arm. Systolic blood pressure was measured in each arm once, and the average of the 2 measurements was obtained. Systolic blood pressure was measured twice in each foot, and an average was taken of the 2 readings from each foot. From this, an ABI was obtained for each leg. Subjects with a resting ABI of less than 0.9 in either leg were classified as having PAD.
Table 1. Baseline Characteristics of 5781 Participants According to PAD Disease Status*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall Cohort (n=5781)</th>
<th>Men With PAD (n=358)</th>
<th>Men Without PAD (n=5423)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, mean (SD)</td>
<td>73.5 (5.8)</td>
<td>77.0 (6.0)</td>
<td>73.3 (5.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>White</td>
<td>5172 (89)</td>
<td>303 (85)</td>
<td>4869 (90)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>230 (4)</td>
<td>33 (9)</td>
<td>197 (4)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>379 (7)</td>
<td>22 (6)</td>
<td>357 (7)</td>
<td></td>
</tr>
<tr>
<td>Self-reported health status excellent or good,† n (%)</td>
<td>4991 (86)</td>
<td>263 (73)</td>
<td>4728 (87)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PASE score, mean (SD)</td>
<td>147 (68)</td>
<td>124 (69)</td>
<td>149 (68)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Walks for exercise, n (%)</td>
<td>2893 (50)</td>
<td>149 (42)</td>
<td>2744 (51)</td>
<td>0.001</td>
</tr>
<tr>
<td>Smoking status, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current</td>
<td>192 (3)</td>
<td>34 (9)</td>
<td>158 (3)</td>
<td></td>
</tr>
<tr>
<td>Past</td>
<td>3412 (59)</td>
<td>235 (66)</td>
<td>3177 (59)</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>2176 (38)</td>
<td>89 (25)</td>
<td>2087 (38)</td>
<td></td>
</tr>
<tr>
<td>Alcohol intake (drinks/wk), mean (SD)</td>
<td>4.3 (6.7)</td>
<td>4.4 (8.0)</td>
<td>4.3 (6.6)</td>
<td>0.01</td>
</tr>
<tr>
<td>Cardiovascular disease, n (%)</td>
<td>1169 (20)</td>
<td>128 (36)</td>
<td>1041 (19)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>2475 (43)</td>
<td>227 (63)</td>
<td>2248 (41)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease, n (%)</td>
<td>610 (11)</td>
<td>57 (16)</td>
<td>553 (10)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>818 (15)</td>
<td>99 (29)</td>
<td>719 (14)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Falls in past year, n (%)</td>
<td>1267 (21)</td>
<td>97 (27)</td>
<td>1110 (20)</td>
<td>0.003</td>
</tr>
<tr>
<td>Inability to rise from a chair, n (%)</td>
<td>149 (3)</td>
<td>23 (6)</td>
<td>126 (2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Any fracture since age 50 y, n (%)</td>
<td>1411 (24)</td>
<td>98 (27)</td>
<td>1313 (24)</td>
<td>0.17</td>
</tr>
<tr>
<td>Statin use, n (%)</td>
<td>1516 (27)</td>
<td>134 (39)</td>
<td>1382 (27)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Thiazide diuretic use, n (%)</td>
<td>706 (13)</td>
<td>64 (19)</td>
<td>642 (12)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Loop diuretic use, n (%)</td>
<td>257 (5)</td>
<td>49 (14)</td>
<td>208 (4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Baseline BMI, kg/m², mean (SD)</td>
<td>27.4 (3.8)</td>
<td>26.8 (3.9)</td>
<td>27.4 (3.8)</td>
<td>0.007</td>
</tr>
<tr>
<td>Percentage weight change from baseline, mean (SD)</td>
<td>−1.6 (5.5)</td>
<td>−3.3 (6.0)</td>
<td>−1.5 (5.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>eGFR (MDRD index), mL·min⁻¹·1.73 m², mean (SD)</td>
<td>77 (18)</td>
<td>70 (22)</td>
<td>77 (18)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Baseline total hip BMD, g/cm², mean (SD)</td>
<td>0.96 (0.14)</td>
<td>0.93 (0.16)</td>
<td>0.96 (0.14)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

PASE indicates Physical Activity Scale for the Elderly; BMI, body mass index; eGFR, estimated glomerular filtration rate; and MDRD, Modification of Diet in Renal Disease.

*PAD defined by ABI <0.90.
†Perceived health status excellent or good vs fair, poor, or very poor.

secondary analyses, we classified ABIs of 0.70 to 0.89 as mild disease, 0.41 to 0.69 as moderate disease, and ≤0.4 as severe disease. For the latter category, none of the participants had ABI levels in the range of severe disease.

Other Measurements

Participants completed a questionnaire and were interviewed at the baseline examination. Race/ethnicity was based on self-declaration. In addition to questions about race/ethnicity, participants were asked about age; health status; physical activity, including completion of the Physical Activity Scale for the Elderly (PASE); use of walking for exercise; social habits; and past medical history. Participants were asked to bring with them to the clinic all current prescription medications used daily or almost daily for at least the past month for verification of use.

Participants were classified as diabetic if they had a fasting (≥8 hours) glucose level ≥126 mg/dL or prevalent self-reported diabetes mellitus at baseline or were using hypoglycemic agents or insulin at baseline. Tests of physical function included inability to rise from a chair (without using arms) 5 times. Weight change was calculated by subtracting weight at the baseline examination from weight at the second examination and was expressed as a percentage of the baseline value. Body mass index was calculated with weight (kg)/height (m²). Participants’ renal function was assessed by estimating the glomerular filtration rate based on the Modified Diet in Renal Disease equation.55

Statistical Analysis

To compare characteristics at the baseline examination by category of PAD (no PAD [ABI ≥0.9] versus PAD [ABI <0.9]), χ² tests were used for categorical variables (Fisher exact tests for categorical data with low expected cell counts), t tests were used for normally distributed continuous data, and Wilcoxon rank sum tests were used for skewed continuous data. For the primary analysis examining the association between PAD and rate of change in BMD at the total hip and its subregions (femoral neck, trochanter), the annualized mean change in BMD and its 95% confidence interval (CI) were calculated for men with and without PAD by the least square means procedure. Known risk factors for bone loss and characteristics related to PAD were examined for inclusion in multivariable models for the associations between PAD and rate of change in BMD. We included in our multivariable models age, race, site, baseline hip BMD, and those variables that were related to PAD at P≤0.10 and rate of change in BMD at P≤0.10, independent of age (ie, self-reported health status, walks for exercise, smoking status, alcohol use, cardiovascular disease, hypertension, diabetes mellitus, loop diuretic use, weight change, inability to rise from a chair, and estimated glomerular filtration rate [Modified Diet in Renal Disease index]).
In secondary analyses, the least squares means procedure was used to compare adjusted mean annualized percentage change in BMD according to PAD severity (moderate versus mild versus no PAD), with results presented as adjusted means and 95% CI and P for trend across the 3 categories. Because high levels of ABI may be indicative of underlying vascular calcification,16–20 and because vascular calcification has been associated with osteoporosis and bone loss,21 we also examined the mean annualized percent change in BMD by decile of ABI to further characterize rate of change in BMD at the extremes of ABI.

Adjusted Cox proportional hazards models were used to analyze the association between baseline PAD status and subsequent risk of nonspine fracture and hip fracture, with results presented as hazard ratios and 95% CIs. We included in our multivariable models age, race, site, and those variables that were related to PAD at the extremes of ABI.

Adjusted Cox proportional hazards models were used to analyze the association between baseline PAD status and subsequent rates of change in hip BMD, 189 (4.4%) had PAD at baseline. Among the 169 men with baseline PAD who did not complete repeat hip BMD measurements, 82 (52 men with mild PAD and 30 with moderate PAD) had died, 12 (7 with mild PAD and 5 with moderate PAD) terminated their participation in the study, and 67 (44 with mild PAD and 23 with moderate PAD) did not attend the second examination, primarily owing to poor health.

### PAD and Rates of Change in Hip BMD
Average rates of change in BMD at the total hip and subregions according to PAD status are shown in Table 2. On average, men with PAD had a higher rate of bone loss at the total hip than men without PAD (−0.78% versus −0.33% per year, P<0.001). The association was only slightly diminished after adjustment for age, race, clinical site, and baseline total hip BMD (−0.66% versus −0.34% per year, P<0.001). After further adjustment for multiple potential confounders, the difference was attenuated but remained significant (−0.49% versus −0.35% per year, P=0.02).

At the femoral neck, the mean annualized rate of bone change in the multivariable model was −0.60% per year (95% CI −0.76 to −0.43) and −0.32% per year (95% CI −0.34 to −0.28) for men with and without PAD, respectively (P=0.001). Mean annualized percent rates of change in hip BMD by severity of PAD are shown in Table 3. We did not find evidence of a graded association between PAD severity and rate of hip bone loss.

We determined mean annualized percent rates of change in total hip BMD by decile of ABI. Evidence was found that the adjusted rate of hip bone loss was greater among men in decile 1 (ABI <0.99, mean loss −0.61% per year) and among men in decile 1 (ABI ≥1.33, mean loss −0.40% per year) than among men in the intermediate deciles 2 to 9 (ABI 0.99 to 1.33, mean loss −0.32% per year; P<0.001 for decile 1 versus deciles 2 to 9 and P=0.07 for decile 10 versus deciles 2 to 9). Rates of loss were similar among men in the intermediate deciles (P>0.16 for comparisons between deciles).

### Results

**Characteristics of the Study Population**
Baseline characteristics of the 5781 men according to PAD status are shown in Table 1. Of the 5781 men in the cohort, 358 (6.2%) had evidence of PAD as defined by an ABI <0.9, including 242 men with mild PAD (ABI 0.70 to 0.89) and 116 with moderate PAD (ABI 0.41 to 0.69; Table 1).

Of the 703 men in the cohort, 703 (12%) did not return for visit 2. The percentage of men who did not return for visit 2 increased with PAD severity: 11% of men without PAD did not return for visit 2 versus 28% among men with mild PAD and 32% among men with moderate PAD (P<0.001). Of the 4302 men with initial and follow-up hip BMD measurements an average of 4.6 years later who were included in the analysis that examined the association between baseline PAD status and subsequent rates of change in hip BMD, 189 (4.4%) had PAD at baseline. Among the 169 men with
Table 3. Mean Annualized Percentage Change in BMD (95% CI) According to Severity of PAD and Hip Region

<table>
<thead>
<tr>
<th>Hip Region</th>
<th>ABI</th>
<th>Unadjusted model</th>
<th>Adjusted for age, race, site, and baseline total hip BMD</th>
<th>Multivariable model*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total hip</td>
<td></td>
<td>-0.65 (-0.88, -0.42)</td>
<td>-0.84 (-0.99, -0.69)</td>
<td>-0.33 (-0.36, -0.31)</td>
</tr>
<tr>
<td>Femoral neck</td>
<td></td>
<td>-0.52 (-0.74, -0.29)</td>
<td>-0.71 (-0.86, -0.57)</td>
<td>-0.34 (-0.36, -0.31)</td>
</tr>
<tr>
<td>Trochanter</td>
<td></td>
<td>-0.36 (-0.59, -0.13)</td>
<td>-0.54 (-0.68, -0.40)</td>
<td>-0.35 (-0.37, -0.32)</td>
</tr>
</tbody>
</table>

Multivariate model* Adjusted for age, race, clinic site, health status, walks for exercise, smoking, alcohol, cardiovascular disease, hypertension, diabetes mellitus, loop diuretic use, weight change, inability to rise from a chair, estimated glomerular filtration rate (Modification of Diet in Renal Disease index), and baseline hip, femoral neck, or trochanter BMD.

PAD and Fractures

During a mean follow-up of 5.4 years (SD 1.4 years), 42 men with PAD (12%), including 17 with moderate PAD (15%) and 25 with mild PAD (10%), experienced at least 1 nonspine fracture compared with 431 (8%) men without PAD. After adjustment for age, site, and race, men with PAD relative to those without PAD had a 1.5-fold increase (hazard ratio 1.47, 95% CI 1.07 to 2.04) in risk of nonspine fracture (Figure 2).

![Figure 2](https://example.com/figure2.png)

Figure 2. Adjusted risk of nonspine and hip fractures for men with PAD compared with men without PAD. COPD indicates chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; PASE, Physical Activity Scale for the Elderly; and CVD, cardiovascular disease.
Further individual adjustment for several additional covariates only modestly attenuated the association.

During a mean follow-up of 5.6 years (SD 1.2 years), 12 men with PAD (3%), including 6 with moderate PAD (5%) and 6 with mild PAD (2%), experienced at least 1 hip fracture compared with 76 men without PAD (1%). After adjustment for age, site, and race, men with PAD relative to those without PAD had a 1.6-fold increase (hazard ratio 1.60, 95% CI 0.86 to 2.99) in risk for first hip fracture, which did not reach statistical significance (Figure 2). Further individual adjustment for several additional covariates did not substantially alter the magnitude of the point estimate of the association, with the exception of baseline hip BMD and inability to rise from a chair 5 times (without using the arms). After adjustment for age, hip BMD, and inability to rise from a chair, no evidence was found of an association between PAD and risk of hip fracture (hazard ratio 1.1, 95% CI 0.57 to 2.13).

Discussion

We found that PAD among community-dwelling older men was independently associated with higher rates of hip bone loss. This association remained after adjustment for several potential confounders. Although our power was limited in examining the association between PAD and risk of hip fracture, the present findings suggest that an association between PAD and hip fracture in older men is primarily explained by older age, lower hip BMD, and poorer lower-extremity performance among men with PAD.

These findings are generally consistent with those reported from prior population-based studies that have examined the cross-sectional association between PAD and BMD.8,22–24 One cross-sectional study of nearly 4000 Chinese men and women 65 to 92 years of age reported that PAD (prevalence 6.8%) was negatively correlated with total hip BMD in the unadjusted analyses, but the correlation was greatly reduced after adjustment for potential confounders.24 In addition, prior studies, including those based on cross-sectional and longitudinal data, have evaluated the association between low bone mass and subclinical atherosclerosis (ie, calcification of coronary or aortic arteries) in various populations, particularly women and minorities.7,21,24,25 In general, these studies have reported an inverse relationship between BMD and calcification of the aorta7,25,26 and coronary arteries.27 In 1 longitudinal study,7 the progression of aortic calcification was linked to higher rates of trabecular bone loss at the spine in postmenopausal women.

An association between PAD and higher rates of bone loss may exist for several reasons. Risk factors for atherosclerosis and osteoporosis overlap. Notably, older age, physical inactivity, smoking, and diabetes mellitus have been linked to both atherosclerosis and osteoporosis. In addition, adults with type II diabetes mellitus are more likely to have PAD than nondiabetic adults.16,28 and increasing evidence suggests that older adults with type II diabetes mellitus have higher rates of bone loss.29–31 Although the association between PAD and higher rates of bone loss among older men in the present study was attenuated after adjustment for these and other potential confounders, an independent association between PAD and higher rates of hip bone loss remained. Aside from shared clinical risk factors, shared biological pathways32–34 may explain the link between PAD, bone loss, and fracture risk. For example, reduced renal function has been linked to both PAD35,36 and higher rates of bone loss and increased risk of fracture7,37; however, in the present cohort, the association between PAD and higher rates of bone loss remained despite adjustment for renal function. In addition, higher levels of inflammatory markers, including homocysteine, C-reactive protein, and interleukin-6, have been linked to both PAD39–41 and higher rates of bone loss and increased risk of fractures.42–47

The present findings also suggest that high ABI, a marker of vascular calcification and increased vessel stiffness, may be associated with increased rates of hip bone loss. Prior studies of vascular calcification and osteoporosis have primarily been conducted in women, but those that have included men have been cross-sectional in design and have not reported an independent association between vascular calcification and lower BMD in men.21,48,49

Using prospective data, we demonstrate an association between PAD and risk of fracture in older men. The association between PAD and increased risk of nonspine fracture was not altered substantially despite adjustment for several potential confounders.

The present study has several strengths, including its prospective design, enrollment of community-dwelling older men not selected on the basis of PAD or low BMD, an objective assessment of atherosclerosis of the lower extremities, and nearly complete ascertainment of incident fractures blinded to PAD status. However, the present study is not without limitations. First, the participants were predominantly white men, such that the results of the present study may not be generalizable to more racially diverse populations or older women. The present results on the relationship between PAD and higher rates of bone loss may underestimate this association, because men with PAD compared with those without were more likely to not return to the clinic for repeat hip BMD measurements, usually because of death in the interim or poor health. We also did not observe a graded association between PAD severity and rates of bone loss; however, because men with moderate to severe PAD were more likely to be missing a repeat BMD measurement than those with mild PAD, our power was limited to detect this relationship. Besides renal function, we were not able to examine potential biological markers that may mediate the association between PAD, bone loss, and fracture. The present findings are limited to PAD as defined by the ABI. We did not use other methods (eg, pulse volume recordings) to determine the presence of disease. Also, we did not perform repeat ABI measurements at the second examination, which prevented us from examining whether progression of PAD was concurrently associated with increasing rates of bone loss. Finally, we did not measure biomarkers such as vitamin D level; additional adjustment for vitamin D levels may have further attenuated the association of PAD with rates of bone loss and fracture.

In conclusion, community-dwelling older men with PAD have higher rates of hip bone loss and an increased risk of

Discussion

We found that PAD among community-dwelling older men was independently associated with higher rates of hip bone loss. This association remained after adjustment for several potential confounders. Although our power was limited in examining the association between PAD and risk of hip fracture, the present findings suggest that an association between PAD and hip fracture in older men is primarily explained by older age, lower hip BMD, and poorer lower-extremity performance among men with PAD.

These findings are generally consistent with those reported from prior population-based studies that have examined the cross-sectional association between PAD and BMD.8,22–24 One cross-sectional study of nearly 4000 Chinese men and women 65 to 92 years of age reported that PAD (prevalence 6.8%) was negatively correlated with total hip BMD in the unadjusted analyses, but the correlation was greatly reduced after adjustment for potential confounders.24 In addition, prior studies, including those based on cross-sectional and longitudinal data, have evaluated the association between low bone mass and subclinical atherosclerosis (ie, calcification of coronary or aortic arteries) in various populations, particularly women and minorities.7,21,24,25 In general, these studies have reported an inverse relationship between BMD and calcification of the aorta7,25,26 and coronary arteries.27 In 1 longitudinal study,7 the progression of aortic calcification was linked to higher rates of trabecular bone loss at the spine in postmenopausal women.

An association between PAD and higher rates of bone loss may exist for several reasons. Risk factors for atherosclerosis and osteoporosis overlap. Notably, older age, physical inactivity, smoking, and diabetes mellitus have been linked to both atherosclerosis and osteoporosis. In addition, adults with type II diabetes mellitus are more likely to have PAD than nondiabetic adults.16,28 and increasing evidence suggests that older adults with type II diabetes mellitus have higher rates of bone loss.29–31 Although the association between PAD and higher rates of bone loss among older men in the present study was attenuated after adjustment for these and other potential confounders, an independent association between PAD and higher rates of hip bone loss remained. Aside from shared clinical risk factors, shared biological pathways32–34 may explain the link between PAD, bone loss, and fracture risk. For example, reduced renal function has been linked to both PAD35,36 and higher rates of bone loss and increased risk of fracture7,37; however, in the present cohort, the association between PAD and higher rates of bone loss remained despite adjustment for renal function. In addition, higher levels of inflammatory markers, including homocysteine, C-reactive protein, and interleukin-6, have been linked to both PAD39–41 and higher rates of bone loss and increased risk of fractures.42–47

The present findings also suggest that high ABI, a marker of vascular calcification and increased vessel stiffness, may be associated with increased rates of hip bone loss. Prior studies of vascular calcification and osteoporosis have primarily been conducted in women, but those that have included men have been cross-sectional in design and have not reported an independent association between vascular calcification and lower BMD in men.21,48,49

Using prospective data, we demonstrate an association between PAD and risk of fracture in older men. The association between PAD and increased risk of nonspine fracture was not altered substantially despite adjustment for several potential confounders.

The present study has several strengths, including its prospective design, enrollment of community-dwelling older men not selected on the basis of PAD or low BMD, an objective assessment of atherosclerosis of the lower extremities, and nearly complete ascertainment of incident fractures blinded to PAD status. However, the present study is not without limitations. First, the participants were predominantly white men, such that the results of the present study may not be generalizable to more racially diverse populations or older women. The present results on the relationship between PAD and higher rates of bone loss may underestimate this association, because men with PAD compared with those without were more likely to not return to the clinic for repeat hip BMD measurements, usually because of death in the interim or poor health. We also did not observe a graded association between PAD severity and rates of bone loss; however, because men with moderate to severe PAD were more likely to be missing a repeat BMD measurement than those with mild PAD, our power was limited to detect this relationship. Besides renal function, we were not able to examine potential biological markers that may mediate the association between PAD, bone loss, and fracture. The present findings are limited to PAD as defined by the ABI. We did not use other methods (eg, pulse volume recordings) to determine the presence of disease. Also, we did not perform repeat ABI measurements at the second examination, which prevented us from examining whether progression of PAD was concurrently associated with increasing rates of bone loss. Finally, we did not measure biomarkers such as vitamin D level; additional adjustment for vitamin D levels may have further attenuated the association of PAD with rates of bone loss and fracture.

In conclusion, community-dwelling older men with PAD have higher rates of hip bone loss and an increased risk of
nonspine fractures. These findings suggest that PAD should be added to the list of secondary medical conditions such as Parkinsonism and stroke that are associated with a greater likelihood of higher rates of bone loss and fracture among older people. Future research should examine potential biological mechanisms underlying this association.

Acknowledgments

We would like to acknowledge Kyle A. Moen for his assistance in preparation of the manuscript and formatting of the tables and figures.

Sources of Funding

The Osteoporotic Fractures in Men (MrOS) Study is supported by National Institutes of Health funding. The following institutes provide support: the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), the National Institute on Aging (NIA), the National Center for Research Resources (NCRR), and the National Institutes of Health Roadmap for Medical Research under the following grant numbers: U01 AR45580, U01 AR45614, U01 AR45632, U01 AR45647, U01 AR45654, U01 AR45583, U01 AG18197, U01 AG027810, and UL1 RR024140; as well as the American Diabetes Association (principal investigator: Dr. Strotmeyer; 1-04-JF-46).

Disclosures

Dr Collins is a member of the Data and Safety Monitoring Committee for Synteract/ViroMed. The remaining authors report no conflicts.

References

Fractures related to osteoporosis and peripheral arterial disease are major causes of morbidity and mortality in older people. Previous large observational studies have provided evidence of an association between bone loss and either incident cardiovascular disease or subclinical atherosclerosis. Evidence also exists to support an association between atherosclerosis of peripheral vessels and osteoporosis. Using the ankle-brachial index and initial and repeat hip bone mineral density in a cohort of community-dwelling men 65 years of age and older in the Osteoporotic Fractures in Older Men (MrOS) study, we found that men with peripheral arterial disease have higher rates of hip bone loss and an increased risk of nonspine fractures. These findings suggest that peripheral arterial disease should be added to the list of secondary medical conditions that are associated with a greater likelihood of higher rates of bone loss and fracture among older people. Future research should examine potential biological mechanisms underlying this association.
Peripheral Arterial Disease Is Associated With Higher Rates of Hip Bone Loss and Increased Fracture Risk in Older Men

Tracie C. Collins, Susan K. Ewing, Susan J. Diem, Brent C. Taylor, Eric S. Orwoll, Steven R. Cummings, Elsa S. Strotmeyer and Kristine E. Ensrud
for the Osteoporotic Fractures in Men (MrOS) Study Group

_Circulation_. 2009;119:2305-2312; originally published online April 20, 2009;
doi: 10.1161/CIRCULATIONAHA.108.820993

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2009 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/119/17/2305

---

**Permissions:** Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

**Reprints:** Information about reprints can be found online at:
http://www.lww.com/reprints

**Subscriptions:** Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org/subscriptions/