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ORIGINAL ARTICLE

Peripheral arterial disease and osteoporosis in older adults: the Rancho Bernardo Study

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Abstract
Summary We examined the association between peripheral arterial disease (PAD) and bone health in 1,332 adults. We found a weak association between PAD and osteoporosis and bone loss only in women, but the association was not independent of age. PAD was not associated with fractures in this community-based population.
Introduction Increased rates of osteoporosis have been reported in patients with cardiovascular disease, suggesting a link between osteoporosis and atherosclerosis.
Methods We examined the association between PAD and bone health in 1,332 adults who attended a research visit in 1992–1996, when the ankle–brachial index (ABI), bone mineral density (BMD), and spine X-rays were obtained. A total of 837 participants attended a follow-up visit in 1997–2000.
Results PAD defined by an ABI≤0.90 was present in 15.4% of the women and 13.3% of the men. Prevalence of osteoporosis was significantly higher in women with PAD compared to women without PAD ($p<0.05$). During an average 4-year follow-up, women with PAD had a significantly higher rate of bone loss than women without PAD ($p=0.05$). The associations were no longer significant after age adjustment. In men, PAD was not associated with osteoporosis, but men with PAD had lower BMD at the femoral neck than men without PAD ($p=0.03$). PAD was not associated with osteoporotic fractures in either sex.
Conclusion We found a weak and age-dependent association between PAD and osteoporosis in women but not men. PAD was not associated with fractures in this community-based population.

Keywords Osteoporosis · Peripheral artery disease

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Introduction

Increased rates of bone loss, osteoporosis, and osteoporotic fractures have been reported in adults with cardiovascular disease, suggesting an association between osteoporosis and atherosclerosis [1–3]. A few studies have suggested an association between osteoporosis and peripheral arterial disease (PAD) in women [4–6], but studies in men yielded inconsistent results [5, 7]. Low bone mineral content at menopause appears to be a risk factor for increased cardiovascular disease mortality in later life [8–10]. To our knowledge, the association of PAD with osteoporotic fractures has not been reported. We report here a study examining the association between PAD based on the ankle–brachial index (ABI), with measures of bone health assessed by dual energy X-ray absorptiometry (DXA) and

fracture status in a large population-based sample of older men and women. The aims of this study were: (1) to determine whether PAD defined by several ABI cut points is associated with low bone mineral density (BMD), bone loss, and/or osteoporotic fractures; (2) to determine whether PAD can predict BMD loss or incident osteoporotic fractures; and (3) to determine whether any associations are independent of age, body mass index (BMI), and other covariates including smoking, physical activity, alcohol intake, medication use, lipid levels, blood pressure, renal function, and diabetes status.

Methods

The Rancho Bernardo Study, a cohort of Caucasian, middle to upper-middle class, community-dwelling adults in Southern California, was established in 1972; details of the initial study have been published [11]. Between 1992 and 1996, approximately 80% (n=1,778) of surviving local residents participated in a research clinic visit. A total of 527 men and 805 women, aged 30 to 97 (mean age=73.8, SD=9.2) completed standardized questionnaires about medical history, including osteoporotic fractures and were examined for ABI and BMD. Seventy-seven percent (n=1,096) of surviving participants returned for a follow-up visit in 1997–2000. Of these, 322 men and 515 women had BMD measurement repeated and were queried about interim OP fractures. Main reasons for nonparticipation among survivors included moving away, being too sick or too busy, or being institutionalized.

Data on the following variables were collected at baseline: age, height, weight, alcohol intake (drink alcohol three or more times/week), smoking status (current vs. not current), medications, physical activity (exercise three or more times/week), history of bone fractures and diabetes, fasting lipid levels, renal function, intermittent claudication (a symptom of severe PAD) based on the Rose questionnaire [12], BMD, and ABI (see below). Radiographs of the thoracic and lumbar spine were obtained and read by a single skeletal radiologist. Serum creatinine levels were measured by Smith Kline Beecham clinical laboratories. Creatinine clearance was calculated by the modified Cockcroft–Gault formula: [140 − age (in years)] × weight (in kilograms) / [72 × serum creatinine (mg/dl)] and corrected for body surface area. For women, the product was multiplied by 0.85 (a correction factor recommended for females) [13].

BMD was measured at the hip and lumbar spine using DXA (Hologic QDR model 1000; Hologic Inc., Bedford, MA, USA). Total hip BMD included the greater trochanter, femoral neck, and intertrochanter area. Bone densitometers were calibrated daily and measurements maintained within the manufacturers' precision standards. The BMD T scores were expressed in standard deviations using the peak bone mass from the manufacturer's reference population. Osteoporosis was defined as BMD at the femoral neck or the hip ≥2.5 standard deviations (SD) below the young adult mean.

Incident fractures and repeated BMD were determined at a follow-up visit an average of 4 years (range 1–7) later. Bone change was calculated as BMD percent change per year. Non-vehicular accident fractures occurring after age 45 were classified as osteoporotic. Ninety-five percent of self-reported fractures were confirmed by radiology reports.

ABI measurements

The ABI is a simple noninvasive method to assess the presence and extent of atherosclerosis in the lower leg. Participants were rested in the supine position for 5 min, after which a specially trained and certified nurse used a handheld Doppler flowmeter attached to a mercury sphygmomanometer cuff to measure the blood pressure in each arm (brachial artery) and leg (posterior tibial artery). Systolic blood pressure was recorded once for each arm and twice for each leg. The ABI was calculated for each leg by dividing the higher systolic pressure of the leg by the systolic blood pressure in the arm. The lower of these two ABIs was used to define participants with PAD. The sensitivity and specificity of an ABI>0.9 for PAD are 80% and 95%, respectively [14]. One man and one woman had an ABI>1.3, consistent with noncompressible arteries and were excluded from the analyses.

Statistical analyses

Descriptive analyses are expressed as mean (SD) or percentages and were compared using the Student t test or chi-square tests as appropriate. Analysis of covariance was used to calculate sex- and site-specific mean BMD levels and mean annual percent change in BMD stratified by PAD status (defined as ABI>0.9 vs. ABI≤0.9 and using literature suggested cut-points of <0.90, 0.90–1.00, 1.01–1.10, and >1.10) [15]. Risk factors previously shown to be associated with BMD in this cohort (age, BMI, use of calcium supplements (yes/no), exercise (≥3/week), renal function, and hormone therapy use (current vs. not) as well as classic risk factors for atherosclerosis and PAD (smoking, hypertension, systolic blood pressure, TC/HDL ratio, and diabetes) were examined in separate and multivariate models. Adjustments for other possible confounders including use of thiazides, vitamin D supplements, and lipid-lowering medication did not change any of the results and were not included in the final models. Adjusted multiple

Table 1 Baseline characteristics by sex and ankle–brachial index groups

	Men					Women				
	ABI>0.9 (n=456)		ABI≤0.90 (n=70)		P value	ABI>0.9 (n=680)		ABI≤0.90 (n=124)		P value
	Mean (SD)	Percentage (%)	Mean (SD)	Percentage (%)		Mean (SD)	Percentage (%)	Mean (SD)	Percentage (%)	
Age (years)	73.2 (8.7)		76.9 (9.0)		0.001	73.2 (9.0)		77.1 (11.3)		<0.001
BMI (kg/m^2)	26.2 (3.6)		25.4 (3.4)		0.10	24.7 (4.0)		24.1 (4.2)		0.16
SBP (mmHg)	136.7 (20.4)		142.4 (20.7)		0.03	138.6 (21.8)		145.7 (24.6)		0.001
Lipids										
Triglycerides	128.3 (86.7)		141.5 (136.8)		0.28	127.8 (70.7)		136.7 (77.0)		0.21
Total cholesterol	196.8 (34.6)		200.2 (39.4)		0.46	215.5 (35.7)		217.1 (40.4)		0.66
LDL	124.4 (29.6)		121.4 (34.0)		0.45	126.5 (33.1)		131.1 (40.0)		0.17
HDL	48.9 (13.8)		49.7 (13.5)		0.67	65.3 (17.1)		60.4 (15.9)		0.003
TC/HDL	4.28 (1.2)		4.27 (1.4)		0.98	3.5 (1.1)		3.8 (1.3)		0.003
Renal function										
CrCl[a]	59.08 (57.6)		53.74 (49.88)		0.011	57.34 (56.1)		52.43 (49.6)		0.002
Lifestyle										
Exercise ≥3/week		79.3		67.1	0.02		72.2		59.7	0.005
Current smoker		4.6		14.3	0.001		7.2		11.3	0.12
Alcohol use ≥3/week		55.4		50.0	0.40		41.7		30.6	0.02
Medications										
Estrogen		–		–	–		42.9		30.6	0.01
Calcium supp		21.5		8.6	0.01		51.5		36.3	0.002
Vitamin D supp		8.8		4.3	0.20		20.0		15.3	0.23
Thiazides		8.4		10.1	0.62		7.8		6.5	0.62
Lipid lowering		11.7		14.5	0.51		12.6		14.8	0.52
Beta blockers		10.1		13.4	0.40		11.2		13.8	0.42
Calcium channel blocker		16.8		19.4	0.81		12.6		14.7	0.54
Medical history										
Hypertension		70.5		74.3	0.52		70.9		79.0	0.06
Diabetes		9.2		15.7	0.09		5.6		9.7	0.08
Chronic Kidney Disease[b]		41.7		56.7	0.021		64.5		75.4	0.021

[a] Creatinine clearance by the Cockcroft-Gault equation

[b] Defined as CrCl < 60 ml/min/1.73 m^2

Table 2 Unadjusted bone mineral density, bone change, and prevalence of osteoporosis and fractures by sex and ankle–brachial index groups

	MEN					WOMEN				
	ABI>0.9 (n=456)		ABI≤0.90 (n=70)		P value	ABI>0.9 (n=680)		ABI≤0.90 (n=124)		P value
	Mean (SD)	Percentage (%)	Mean (SD)	Percentage (%)		Mean (SD)	Percentage (%)	Mean (SD)	Percentage (%)	
BMD										
Total hip	0.953 (0.149)		0.928 (0.163)		0.19	0.797 (0.137)		0.771 (0.143)		0.06
Femoral neck	0.760 (0.134)		0.722 (0.130)		0.03	0.653 (0.112)		0.637 (0.128)		0.15
Bone change[a]										
Total Hip	−0.47 (0.98)		−0.61 (1.37)		0.47	−0.52 (1.26)		−0.86 (1.35)		0.05
Femoral neck	−0.31 (1.50)		−0.45 (1.70)		0.60	−0.33 (1.86)		−0.30 (1.36)		0.88
Osteoporosis										
Total hip		8.1		8.7	0.51		17.6		25.4	0.04
Femoral neck		35.5		43.5	0.20		48.5		59.2	0.03
Fractures										
Vertebral		9.1		2.9	0.08		13.0		14.8	0.60
Nonvertebral[b]		6.9		4.5	0.33		11.6		13.6	0.55
Incident[a,b]		8.6		5.7	0.56		8.5		11.9	0.40

[a] For the 322 men and 515 women who returned for the follow-up visit

[b] Includes fragility fractures at the hip, femur, forearm, and wrist

logistic regression was used to assess the contribution of PAD status to the prevalence and incidence of osteoporotic fractures. Because there were important differences in the prevalence of osteoporosis, bone loss, and PAD between men and women, all analyses were presented stratified by sex. All statistical tests were two-tailed, with statistical significance defined as $p<0.05$. SPSS (SPSS Inc., SPSS Base 15 for Windows User's Guide) and SAS (SAS Institute SAS User's Guide, Version 8.2) were used for analysis.

Results

The mean age was 74 years (SD=9, range 30 to 97). At baseline, PAD defined by an ABI≤0.90 was present in 15.4% of women and 13.3% of men. No participants reported intermittent claudication. Table 1 shows that, compared to those without PAD, men and women with PAD were older ($p<0.001$), more likely to have higher SBP ($p\leq0.03$) and lower levels of creatinine clearance ($p\leq0.01$), more likely to be sedentary ($p\leq0.02$), less likely to report calcium supplementation ($p<0.02$), and more likely to have chronic kidney disease defined as CrCl<60 ml/min/1.73 m^2 ($p=0.02$). Additionally, women with PAD were less likely to be current users of estrogen therapy ($p=0.01$), had a higher TC/HDL ratio ($p=0.003$), and were less likely to report alcohol intake ($p=0.02$) than women without PAD. Men (but not women) with PAD were more likely to be current smokers ($p=0.001$) than men without PAD.

Participants who did not return for the follow-up visit were older (75.8 vs. 72.6 years, $p<0.01$), had lower mean ABI (1.02 vs. 1.06, $p<0.01$) and were more likely to have categorically defined PAD (19.5%1 vs. 11.7% $p<0.001$) when compared to participants who returned for the follow-up visit. They were also more likely to have total hip and femoral neck osteoporosis (18.4% vs. 12.2%, $p=0.002$ and 49.5% vs. 42.1%, $p=0.03$, respectively) but had similar prevalence of vertebral and nonvertebral osteoporotic fractures.

The BMD, BMD change, and prevalent and incident osteoporotic fractures are shown in Table 2. The only statistically significant differences were that men with PAD had lower BMD at the femoral neck ($p=0.03$), and women with PAD had a significantly higher rate of bone loss at the hip (−0.86%/year vs. −0.52%/year, $p=0.05$) when compared to men and women without PAD. Compared to women without PAD, the prevalence of osteoporosis by WHO (*T* score) criteria at the femoral neck and hip was significantly higher in women with PAD (59.2% vs. 48.5% and 25.4% vs. 17.6%, respectively, $p<0.05$). There were no differences in categorically defined osteoporosis prevalence by PAD status in men. All significant associations between PAD and bone were no longer significant after adjusting for age. Further adjustments for BMI, exercise, smoking status, cholesterol/HDL ratio, hypertension, creatinine clearance, and diabetes did not materially change any of the results. Stratifying ABI by quartiles or using three categories (tertiles or ABI<0.9, 0.9–1.1, and >1.1) did not change the significance of the associations (results not shown).

At baseline, 143 participants had reported at least one clinical vertebral fracture and 126 reported a nonvertebral fracture. Incident nonvertebral fractures were reported by 70 participants. More women than men had a vertebral and/or nonvertebral osteoporotic fracture at baseline (13% vs. 8% and 12% vs. 7%, respectively; all $p<0.01$), but there were no sex difference in the incidence of nonvertebral OP fractures (8.2% in men vs. 9.0% in women, $p=0.72$). Logistic regression models (Table 3) show that PAD was not associated with prevalent or incident OP fractures in men or women. After a mean follow-up of 4 years (SD=0.9), BMD was the only independent variable associated with osteoporotic fractures for both sexes with higher BMD

Table 3 Odds ratio for predictors of osteoporotic fractures in men and women

	Nonvertebral fractures	Vertebral fractures	Incident nonvertebral fractures
Men	(*n*=34)	(*n*= 42)	(*n*=26)
ABI<0.9	1.25 (0.36–4.37)	3.33 (0.74–14.9)	1.52 (0.30–7.45)
Age (years)	0.97 (0.92–1.02)	1.01 (0.97–1.07)	1.01 (0.94–1.07)
BMI	1.01 (0.89–1.15)	1.01 (0.88–1.13)	1.16 (1.00–1.35)
Hip BMD	0.18 (0.01–3.20)	0.03 (0.002–0.49)**	0.004 (0.00–0.20)**
Women	(*n*=92)	(*n*=101)	(*n*=44)
ABI<0.9	0.87 (0.47–1.63)	1.47 (0.75–2.87)	0.84 (0.31–2.26)
Age (years)	1.00 (0.97–1.04)	1.06 (1.02–1.10)**	0.98 (0.93–1.03)
BMI	0.99 (0.92–1.07)	1.13 (1.05–1.21)*	1.05 (0.95–1.15)
Hip BMD	0.07 (0.01–0.58)**	0.005 (0.01–0.04)**	0.12 (0.01–2.30)
Current estrogen	1.19 (0.70–2.03)	1.62 (0.92–2.86)	1.05 (0.49–2.22)

Rancho Bernardo Study 1992–1996 and 1999–2002. Multivariable models also included current smoking, lack of exercise, hypertension, diabetes, TC/HDL, and kidney disease—all variables were not significant predictors of fractures

*$p<0.05$, **$p\leq0.01$

associated with fewer prevalent nonvertebral and vertebral fractures in women and prevalent vertebral fractures and incident nonvertebral fractures in men. In women, age and BMI were also associated with clinical vertebral fractures.

Discussion

In this study, PAD defined as an ABI≤0.9 was not independently associated with BMD, osteoporosis, or osteoporotic fractures in either sex. In accord with other studies, hip BMD was an independent risk factor for vertebral and nonvertebral fractures in both sexes [16–20]. The increasing odds for a vertebral fracture with increasing BMI observed in women in this study were unexpected and could be spurious. A high BMI has been shown to protect the bone, and low BMI is a risk factor for osteoporotic fractures in weight-bearing appendicular bones [21, 22], but the effect of BMI on the spine has been less consistent. Three large population-based studies found a weak [23] or absent association [24, 25] between bodyweight and prevalent or incident vertebral fracture in both sexes. In contrast, increasing bodyweight was associated with a reduced risk of a first vertebral fracture in women in the Study of Osteoporotic Fractures [26]. We were unable to examine incident vertebral fractures because X-rays were not obtained in the follow-up visit.

Previous studies examining the cross-sectional association between osteoporosis and PAD have reported weak or absent associations. Vogt and collaborators [27] studied 1,292 women from the Study of Osteoporotic Fractures with a mean age of 71 years and found an association between the ABI and BMD at the femoral neck, but the association was not independent of BMI. Van der Klift and collaborators [5] studied 3,053 women and 2,215 men aged 60 to 70 years from the Rotterdam Study and found that PAD was associated with lower BMD at the femoral neck in women but not in men, with no associations found between PAD and lumbar spine in either sex. Mangiafico and collaborators [4] reported an 18.2% prevalence of PAD in women with osteoporosis versus 3.8% in women with normal BMD; lower BMD at the femoral neck was associated with PAD independent of BMI, smoking, lipid levels, blood pressure, or other risk factors for atherosclerosis.

Different results have been reported from recent small case-control studies of patients with advanced arterial disease. Pennisi and collaborators [28] studied 36 women with advanced atherosclerosis of the carotid and/or femoral artery and 30 age-matched controls and reported that carotid or femoral plaque measured by ultrasonography was associated with both regional and total body BMD. Laroche and collaborators [7] studied 18 men with symptomatic arterial disease of the lower limbs and found a decrease in bone mineral content in the more affected leg compared with the less affected leg. Ischemia was postulated to be the cause of local bone loss in these men with asymmetric PAD. Fahrleitner-Pammer and collaborators [29] examined 95 men and women with angiographically confirmed PAD and 44 controls and found that PAD was associated with lower BMD and increased bone resorption independent of BMI and other known confounders. In our study, the associations between PAD and BMD were weak and age-dependent. It is likely that people with mild or asymptomatic arterial disease do not have sufficient compromised circulation to impair bone health, unlike those in the studies above.

Overall, these data suggest that severe atherosclerosis that compromises blood flow to the lower limb may cause bone loss but that mild usually subclinical PAD does not. In a recent prospective study of 963 postmenopausal women, Tanko and collaborators [30] reported that severity of atherosclerosis in the aorta was inversely associated with BMD at the hip but not at the radius or spine and concluded that the association of aortic calcification with BMD is site-specific. The authors speculated that aortic calcification may influence blood flow to the distal regions affecting blood supply to the hip [31]. In a large prospective study of 3,998 Chinese men and women aged 65 to 92 years, Wong and collaborators [32] reported an association between PAD and BMD at the hip, but, as in our study, this association was not independent of age, sex, bodyweight, and other risk factors. There is evidence that arterial calcification is a strong predictor of low bone mass and fragility fractures, but to our knowledge, no study has examined the association of PAD with prevalent and incident osteoporotic fractures. Patients with PAD may experience difficulties with mobility and proprioception increasing their likelihood of falls and fractures. Although we found no association between PAD and prevalent or incident osteoporotic fractures, there were relatively few fractures limiting our power.

Our study has other limitations. The Rancho Bernardo Study population is almost entirely Caucasian and middle to upper-middle class; results might not generalize to other populations. However, the prevalence of PAD was 15% in women and 13% in men—similar to PAD prevalence reported by other comparable studies [5]. Participants' mean age at baseline was 74 years, and participants who did not return for the follow-up visit were older and more likely to have PAD and osteoporotic fractures. PAD was not assessed by angiography, but others have shown a high validation of ABI with angiographic studies [33]. Finally, the mean follow-up for bone loss and incident fractures was only 4 years, and the incidence of OP fractures was low. A longer follow-up may be needed to better assess the role of PAD in the incidence of OP fractures.

In conclusion, in these relatively healthy older adults, associations were weak and entirely explained by age. Longer, larger prospective studies are needed to determine whether asymptomatic ABI independently predicts bone loss and fractures in older adults. Given the increasing age in the USA, it is important to examine the association between these two chronic conditions and potential common underlying pathophysiologic mechanisms.

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Conflicts of interest None.

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