Increased prevalence of peripheral arterial disease in osteoporotic postmenopausal women

Abstract The aim of this study was to investigate the prevalence and correlates of peripheral arterial disease (PAD) in a population of osteoporotic postmenopausal women. The presence of PAD was assessed by ankle brachial index (ABI) in 345 ambulatory osteoporotic postmenopausal women, and in 360 community-based, age- and race-matched postmenopausal women with normal bone mineral density (BMD) (control group). PAD was detected in 63/345 (18.2%) osteoporotic women and in 14/360 (3.8%) control subjects ($P < 0.0001$). The mean ABI values were significantly lower in the osteoporosis group than in the control group (0.98 ± 0.09 vs. 1.04 ± 0.06, $P < 0.0001$). No difference in cardiovascular risk factors was observed between osteoporotic patients and controls, or between osteoporotic patients with and without PAD. Osteoporotic patients with PAD had lower femoral neck BMD $T$ scores than those without PAD ($-4.2 ± 0.7$ vs. $-2.3 ± 0.7$, $P < 0.0001$). Only 4 PAD patients (5.1%) had intermittent claudication. In multivariate logistic regression analysis, factors independently associated with PAD within osteoporotic patients were lower femoral neck BMD $T$ score (odds ratio (OR) = 0.20, 95% confidence interval (CI), 0.05–0.70, $P = 0.01$) and systolic blood pressure (OR = 1.02, 95% CI, 1.00–1.03, $P = 0.01$). This study shows for the first time an increased prevalence of PAD among osteoporotic postmenopausal women, with a lower femoral neck BMD $T$ score being a significant independent predictor. The findings suggest that vascular status evaluation should be done in osteoporotic postmenopausal women in order to identify candidate patients for preventive and therapeutic cardiovascular interventions.

Key words postmenopausal osteoporosis · peripheral arterial disease · ankle brachial index · bone mineral density

Introduction

Previous studies have suggested an association between osteoporosis and peripheral arterial disease (PAD) [1–4] as well as atherosclerosis at other sites [4–10], although some other studies disagreed [11–13]. Cross-sectional and prospective data from a population-based study [1] have shown that among elderly women, bone mineral density (BMD) at the radius, calcaneus, and hip was positively correlated with the ankle brachial index (ABI), which is an accurate and reliable indicator of PAD [14,15]. In addition, the annual decrease in ABI was associated with an increase in the rate of bone loss at the hip and calcaneus. In the Rotterdam Study, van der Klift et al. [2] found that the risk of PAD, as assessed by an ABI of <0.9, was increased in women, but not in men, with a low femoral neck BMD, whereas no association between PAD and lumbar spine BMD could be observed in either women or men. In the population-based study by Tankó et al. [9] focusing on the relation between BMD and aortic calcification in elderly women, a subgroup of women with a history of intermittent claudication showed a lower hip BMD and more severe aortic calcification than the age-matched controls. A small clinical study in men with symptomatic PAD has demonstrated that the body mineral content of the leg more severely affected by arterial disease was significantly lower than that of the less affected leg [3]. Recently, we found lower total body, lumbar spine, and femoral neck BMD and reduced levels of serum markers of osteoblast formation among women and men with carotid and/or femoral atherosclerotic plaques [4]. However, although the findings from the aforementioned studies provide evidence of a link between low BMD and PAD, no data were obtained in these studies concerning the frequency of PAD in patients with osteoporosis. Therefore, the prevalence and correlates of PAD in postmenopausal women with osteoporosis diagnosed in a clinical setting are unknown. In the present study, we investigated for the first time whether the prevalence of PAD, as assessed by the ABI, is increased in a population of
postmenopausal women with osteoporosis recruited from a clinical setting, as compared with a control group with normal BMD. We also assessed the relation of PAD to traditional risk factors for atherosclerosis in these patients.

**Materials and methods**

Subjects and design

Three hundred and sixty-eight ambulatory, postmenopausal Caucasian women meeting the World Health Organization (WHO) criteria for osteoporosis (BMD T score <−2.5 at the spine and/or femoral neck) [16] were consecutively recruited from the Osteoporosis and Bone Metabolism Clinic at our hospital between February and November 2004. Eighteen patients with secondary causes of osteoporosis were excluded, and 5 patients declined participation in the study for personal reasons. Overall, of the 368 osteoporotic women initially recruited, 345 patients (93.7%), aged 46–78 years, took part in the study. Three hundred and sixty age- and race-matched control subjects with normal bone density (BMD T score ≥−1) were recruited in the same time period as the osteoporotic patients. They were recruited by advertisements in the local community, and were from the same residential areas as the osteoporotic patients. All of them agreed to participate in the study. BMD measurements for potential control subjects and osteoporotic patients were performed using identical procedures at the same hospital osteoporosis center (the Osteoporosis and Bone Metabolism Clinic). We chose to recruit control subjects from the community rather than from the hospital in order to have a control group that was representative of the general population.

Women were considered to be postmenopausal if they had not menstruated for at least 1 year. All postmenopausal women answered a questionnaire regarding their age at menopause, smoking habits, presence of hypertension, diabetes mellitus, hyperlipidemia, preexisting clinical coronary artery disease (angina pectoris, myocardial infarction, coronary revascularization procedures), and cerebrovascular disease (stroke, transient ischemic attack, carotid revascularization procedures), and current and past medication use, such as hormone replacement therapy (HRT) and statin use. Information was also obtained from a review of medical records and laboratory data. Diabetes, hypertension, and hyperlipidemia were defined by current diagnostic criteria [17–19]. These disorders were also considered to be present if the patients were receiving treatment for them. Obesity was defined as a body mass index (BMI) of 30 kg/m² or higher, according to the recommendation of WHO [20]. All participants underwent ABI and BMD measurements, and blood tests for plasma glucose and serum total cholesterol, albumin, calcium, and phosphorus. All subjects were clinically evaluated for intermittent claudication and other symptoms or signs of PAD, and had their height and weight measured to calculate their BMI. The subjects’ blood pressure was measured in both arms with a mercury-column sphygmomanometer. Our institutional ethics committee approved the study, and informed consent was obtained from all study participants.

Ankle brachial index

The ABI was performed by a single observer (E.R.) who was unaware of the BMD readings. Systolic blood pressures were measured using a sphygmomanometric cuff and a hand-held 8-MHz Doppler probe (Hadeco Bidop ES−100V3; Hayashi Denki Kawasaki, Japan) as the subjects were in the supine position, after 5 min rest. The right and left ABI values were calculated by dividing the higher of the dorsalis pedis and posterior tibial systolic pressures in each leg by the higher of the two arm pressures, and the worst of the two values was used to define the ABI for each patient [21]. PAD was defined as an ABI of <0.90 on each leg, which is 95% sensitive and 99% specific for angiographically significant PAD [22]. Participants were excluded from the data analysis if they were found to have an ABI >1.30. Such high values usually indicate calcified, noncompressible, or poorly compressible leg arteries, leading to spuriously high ankle blood pressure values [23].

Bone mineral density

Areal BMD (grammes per centimetre squared; bone mineral content relative to projection area) was measured by dual-energy X-ray absorptiometry (DXA) (Lunar DPXL; Lunar. Madison, WI, USA) at the lumbar spine (L2–L4) and the femoral neck. At these measurement sites, the precision of the method (coefficient of variation, CV) at our laboratory was 0.7% for the lumbar spine and 0.5% for the proximal femur. The results for areal BMD were transformed to T scores (calculated as the difference between the actual measurement and the mean value of healthy gender-matched adult controls, divided by their standard deviation) from the data provided by the densitometer manufacturer.

Biochemical measurements

Blood samples were collected, after a overnight fast, into vacutainer tubes. After separation, plasma and serum aliquots were stored at −20°C until analysis. Plasma glucose and serum total cholesterol were measured enzymatically using the Cobas Integra Roche analyser (Roche Diagnostics, Milan, Italy). Serum calcium, phosphorus, and albumin were determined by colorimetric assays on the Cobas Integra Roche analyser (Roche Diagnostics). Serum calcium was adjusted for albumin concentration.

Statistical analysis

Continuous data are reported as mean ± standard deviation (SD), and categorical data as percentages. Comparisons between groups were made by means of unpaired t-test or