Low Femoral Bone Mineral Density and Quantitative Ultrasound Are Risk Factors for New Osteoporotic Fracture and Total and Cardiovascular Mortality: A 5-Year Population-Based Study of Brazilian Elderly Women

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Background. Prospective and cross-sectional studies have confirmed a significant association between bone mineral density (BMD) measurements and fracture risk. However, the relationship among incident fracture risk, mortality, BMD, and quantitative ultrasound is controversial and less studied.

Methods. At baseline, 275 postmenopausal elderly women were evaluated by clinical questionnaire regarding fracture risk factors and had radiological analysis of the spine, spine and femur dual energy x-ray absorptiometry, and calcaneous quantitative ultrasound measurements. Five years later, 42 (15.3%) women had died, 25 (9.1%) were lost to follow-up, and 208 (75.6%) continued the study. Specific questionnaire items regarding fracture risk were reevaluated, and thoracic and lumbar spine x-rays were taken to identify new fractures. Causes of mortality in this population were also assessed. All reported deaths were confirmed by review of death certificates or hospital records and were classified according to International Classification of Diseases, 10th Revision (ICD-10) code.

Results. After adjustments for age, weight, body mass index, smoking status, previous fracture, physical activity, drug use, and presence of chronic diseases, each 1 standard deviation (SD) reduction in stiffness index (SI) at baseline was significantly associated with future fracture (hazard ratio [HR] = 2.23; 95% confidence interval [CI], 1.30–3.83) and total mortality 5 years later (HR = 1.57; 95% CI, 1.10–2.47). Femoral neck and trochanter BMD values at baseline were also related to new fracture (HR = 2.01; 95% CI, 1.27–3.18 and HR = 1.62; 95% CI, 1.08–2.42, respectively) and total mortality (HR = 1.44; 95% CI, 1.06–2.22 and HR = 1.59; 95% CI, 1.07–2.36, respectively). Cardiovascular mortality was associated with decreased baseline femur BMD (HR = 1.28; 95% CI, 1.08–2.26) and lower SI values (HR = 1.54; 95% CI, 1.08–2.79).

Conclusions. Our results demonstrate that low femoral BMD and low SI are able to predict fracture risk and are related to non-cause-specific and cardiovascular mortality, independently of other factors associated with osteoporosis, death, or aging.

Many prospective studies have shown that bone mineral density (BMD) measurements are able to predict fracture (1–3). However, in some individuals who will fracture, risk fracture will not be identified as high on the basis of their BMD assessment. New techniques have emerged to evaluate other structural properties such as bone quality and microarchitecture with the purpose of improving the identification of patients at risk for osteoporotic fractures. Quantitative ultrasound (QUS) is an alternative method, and its advantages include smaller size, portability, lack of ionizing radiation, lower cost, and simpler use when compared to conventional dual energy x-ray absorptiometry measurements. Moreover, QUS has been proven to be able to predict osteoporotic fractures at any skeletal site, even after adjustments for BMD values (4–7).

Although the prevalence of vertebral deformities and death increases with age, some authors have demonstrated that prior fracture and low BMD measurements are associated with increased mortality risk (8–14). Studies in the elderly population have found a significant relationship between mortality in excess, mostly due to cardiovascular diseases and frailty syndrome, and prevalent and incident osteoporotic fractures, even after statistical adjustments for age and other confounding factors (14–20). The significant correlation among low BMD, osteoporotic fracture, cardiovascular disease, and mortality emphasizes some similarities between vascular and bone pathology. Other authors have confirmed a negative association between BMD measurements and arterial calcification (21–23), suggesting potential biological reasons for the association between osteoporosis and atherosclerosis (24–28).

In the present study, we evaluate clinical performance of BMD and QUS measurements to predict new fractures and mortality in elderly postmenopausal Brazilian women.

Methods

Participants

From 1997 through 1998, a total of 419 postmenopausal Caucasian elderly women were invited to participate in the...
study at the São Paulo Hospital Rheumatology Outpatient Clinics. Two hundred seventy-five women met the study criteria and were enrolled into the first phase of this cohort prospective Brazilian study. At baseline, 122 women (44.4%) had had previous osteoporotic fracture. Baseline characteristics of this population have been published previously (7). Women with potential secondary osteoporosis were excluded. Of the 144 patients that did not meet the study inclusion criteria, 78 (54.2%) were excluded due to potential secondary osteoporosis (patients with thyroid disorders, asthma, renal failure, and prolonged corticosteroid therapy), 45 (31.2%) did not agree to participate in the study, and 21 others (14.6%) were illiterate. Use of medication was not considered an exclusion criterion, even use of those medications known to affect bone metabolism. Patients enrolled in the study were followed up to 5 years to evaluate the performance of different risk factors to predict new osteoporotic fracture and mortality. The study was approved by the São Paulo Hospital’s Ethics Committee, UNIFESP/EPM (Universidade Federal de São Paulo/Escola Paulista de Medicina), and all patients gave informed consent.

Clinical Evaluation and BMD Measurements

All participants were interviewed and underwent a complete clinical examination. Detailed data concerning medical conditions, anthropometric measurements, previous fracture, gynecological history, lifestyle habits, and past and current medication use were evaluated by specific questionnaire and confirmed by chart records.

Lateral radiography of the thoracic and lumbar spine was taken in all patients at baseline and at the last visit 5 years later to identify vertebral fracture. An osteoporotic fracture was defined as a fracture occurring after a fall from standing height or lower. Vertebral fracture was defined according to quantitative and morphometric criteria. Two trained rheumatologists analyzed all radiographs. Inter and intra-observer agreements were 93.7% (κ score = 0.82) and 95.2% (κ score = 0.84), respectively. Prevalent and incident vertebral fractures were identified after comparison with baseline x-ray. Spine and femur BMD (Lunar DPX-L; GE Healthcare Lunar, Madison, WI) were measured in all patients at baseline and at the last visit had significantly lower spine and femur BMD than those who did not sustain a new fracture during the follow-up. Baseline BMD and QUS measurements were classified in sample-based tertiles. Continuous variables were compared by Student’s t test and Pearson’s correlation analysis for statistical significance. Kaplan–Meier survival analysis was performed to evaluate association among risk factors, BMD measurements, incident fracture, and death. Mortality rate and incidence of fracture at the end of the study were derived from the Kaplan–Meier curves.

Sixty-seven patients did not return to the hospital for reevaluation: 42 patients had died, and 25 others were not found (change of address or telephone, migration, etc.). Descriptive analysis of the participants who survived during the study follow-up is detailed in Table 1. Forty-one patients had new osteoporotic fracture during this time (incidence rate = 41.7/1000 person-years) and 42 women (15.3%) died during the follow-up (mortality rate = 36.2/1000 person-years). As expected, women who died or had new fractures during the follow-up were on average older, thinner, and shorter than were survivors or women without new fractures.

Seventy-one new fractures were identified in 41 patients in the second visit. Vertebral fractures were the most frequent (70.4%), followed by nonvertebral fractures (29.6%). Patients with new osteoporotic fractures 5 years after the baseline visit had significantly lower spine and femur BMD and heel QUS values at baseline than those who did not sustain a new fracture during the follow-up. Baseline BMD and QUS measurements for the population are also shown in Table 1. Analyzing death cases in our sample, we observed that the most prevalent causes of death in our population were cardiovascular diseases (57.1%), followed by infectious disorders (19%) and cancer (14.3%).
Current use of medications for osteoporosis was observed in 92 patients (33.5%) at baseline and in 109 women (52.4%) 5 years later. We did not observe, at either visit, any statistically significant difference in the use of drugs between women with fracture and those without. The most prevalent comorbidities reported at the last visit were cardiovascular diseases (26%), rheumatic or endocrine disorders (9.6%), and cancer (3.8%).

Advanced age, low weight, previous fracture, and familial history of hip fracture (FHHF) were the most significant predictors of new osteoporotic fracture in our population. The probability of new fracture at the end of the study was 15% for women 74 years old or older, 20% for women with weight 56 kg or lower, 28% for patients with a previous fracture, and 30% for those with FHHF. Use of medications, comorbidities, physical activity level, and smoking status were not associated with fracture probability.

BMD and QUS measurements taken at baseline were significantly associated with new fracture during the 5-year follow-up period. Lower spine, femoral neck, and trochanter BMD values, as well as lower QUS measurements were all associated with significantly higher probability of incident fractures (Figure 1).

When we analyzed cause of death and its predictors in our sample, similar associations were observed (Figure 2). Lower BMD and QUS measurements taken at baseline were associated with significantly higher mortality risk. Lower values for spine and femur BMD and QUS variables were strongly associated with higher mortality rate. Mortality rate at the end of the study was 28% in women with low trochanter BMD as compared to 5% in those with normal trochanter BMD values. Accordingly, mortality rate at the end of the study was 38% in women with low SI values at baseline as compared to 4% in those with normal SI values. When we analyzed cause-specific mortality, only death due to cardiovascular etiology was associated with low BMD measurements (data not shown). Different from the models described for new fracture and total mortality, low weight and height and sedentary lifestyle were not associated with higher cardiovascular mortality. Smoking tended to increase the risk of cardiovascular mortality.

Women with lower body mass index tended to have higher mortality rate, but that was not statistically significant. As demonstrated in Figure 3, women without current physical activity had significantly higher mortality rates. Prior hormone replacement therapy, concomitant diseases, and smoking status were not correlated with mortality.

Cox proportional hazard regression models demonstrated that low femoral BMD and SI values were associated with higher risk for new osteoporotic fracture and mortality rate (Table 2). After adjustments for age and other potential confounders listed above, each 1 SD reduction in femoral neck BMD led to a 2-fold increase in the risk of new osteoporotic fracture at any skeletal site and to a 1.43- and 1.28-fold increase in total and cardiovascular mortality, respectively. A similar relationship was observed for trochanter BMD measurements, which were associated with significantly higher total and cardiovascular mortality (1.59- and 1.30-fold increase for each 1 SD reduction in trochanter BMD, respectively). We also observed 2.23-, 1.57-, and 1.30-fold increase for each 1 SD reduction in trochanter BMD, respectively. We also observed 2.23-, 1.57-, and 1.30-fold increase for each 1 SD reduction in trochanter BMD, respectively.

Table 1. Anthropometric Data, Medical History, and Bone Mineral Density and Quantitative Ultrasound Values in 208 Survivors Evaluated 5 Years After the Baseline Visit, According to the Presence of New Osteoporotic Fracture

<table>
<thead>
<tr>
<th>Variables</th>
<th>Without New Fracture (N = 167)</th>
<th>With New Fracture (N = 41)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>74.6 ± 6.4</td>
<td>77.6 ± 6.5</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>62.1 ± 9.7</td>
<td>53.2 ± 9.3</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Height, m</td>
<td>1.51 ± 0.07</td>
<td>1.46 ± 0.08</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>BML, kg/m²</td>
<td>27.3 ± 4.1</td>
<td>25 ± 4.49</td>
<td>.08</td>
</tr>
<tr>
<td>Previous fracture</td>
<td>54 (32.3%)</td>
<td>31 (75.6%)</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>FHHF</td>
<td>36 (21.6%)</td>
<td>19 (46.3%)</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Baseline BMD, g/cm²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spine</td>
<td>0.970 ± 0.2</td>
<td>0.790 ± 0.2</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Femoral neck</td>
<td>0.790 ± 0.1</td>
<td>0.660 ± 0.1</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Trochanter</td>
<td>0.680 ± 0.1</td>
<td>0.550 ± 0.1</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Baseline QUS values</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BUA, dB/MHz</td>
<td>105.7 ± 9.1</td>
<td>95.2 ± 6.8</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>SOS, m/s</td>
<td>1525.9 ± 28.7</td>
<td>1494 ± 23.4</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Stiffness index</td>
<td>77.6 ± 12.7</td>
<td>62.3 ± 10</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Note: BMI = body mass index; FHHF = familial history of hip fracture; BMD = bone mineral density; QUS = quantitative ultrasound; BUA = broadband ultrasound attenuation; SOS = speed of sound.

1.54-fold increases in the risk of new fracture, total and cardiovascular mortality for each 1 SD reduction in calcaneous SI, respectively. The presence of dyslipidemia did not mitigate these associations.

Age-adjusted areas under the receiver-operating curve (AUC ROC) demonstrated that the performances of femur BMD and calcaneous QUS measurements to predict the risk of new osteoporotic fracture were similar in our population (Table 3 and Figure 4).

**DISCUSSION**

In this prospective study, we found that low femoral BMD and calcaneous QUS measurements were associated with increased risk of new osteoporotic fracture and mortality rate in elderly women, even after adjustments for age and other potential confounders. For each 1 SD reduction in femoral BMD or SI, the risk of fracture increased 1.5- to 2-fold, respectively. It is interesting that patients with low femoral BMD and QUS measurements at baseline had higher cardiovascular mortality risk evaluated 5 years later. Previous studies have suggested significant association between low BMD measurements, fractures, and non-cause-specific mortality (1–3,5,6,16,17). Only a few studies have suggested significant correlation between low BMD or fractures and atherosclerotic diseases such as coronary heart disease, stroke, and sudden death (14,15,17). The evidence for such association is still preliminary, and the issue remains controversial.

At the end of the study, we observed slightly higher incidence of new osteoporotic fracture than that reported in other populations (2,9,16,30). This observation could be explained by the fact that our sample included patients at higher risk (women, advanced age, Caucasian race, history of prior fracture, high prevalence of FHHF, low BMD and QUS measurements) (7). In contrast, the incidence found in
Figure 1. Cumulative proportion free of subsequent osteoporotic fracture in Brazilian elderly women according to spine bone mineral density (BMD) (A), femoral neck BMD (B), trochanter BMD (C), broadband ultrasound attenuation (BUA) (D), speed of sound (SOS) (E), and stiffness index (F) measurements taken at baseline. Data are adjusted for age, weight, height, body mass index, physical activity, concomitant medications, smoking status, previous fracture, and presence of comorbidities.
Figure 2. Cumulative survival rate in Brazilian elderly women according to spine (A), femoral neck (B), and trochanter (C) bone mineral density (BMD), broadband ultrasound attenuation (BUA) (D), speed of sound (SOS) (E), and stiffness index (F) measurements at baseline. Data are adjusted for age, weight, height, body mass index, physical activity, concomitant medications, smoking status, previous fracture, and presence of comorbidities.
comorbidities (A), level of physical activity (B), osteoporosis (C), and smoking status (D).

Figure 3. Cumulative survival rate in Brazilian elderly women according to level of physical activity (A), use of medications for osteoporosis (B), comorbidities (C), and smoking status (D).

our population for nonvertebral fractures, especially forearm and femur, was lower than that reported in the literature for other populations. Corroborating our findings, Brazilian national data have demonstrated lower incidence of femoral fracture when compared to North American and European populations (31).

Likewise, the total mortality incidence in our sample was significantly higher than the mortality rate reported for the greater São Paulo area (32). The inclusion criteria used for this study and the characteristics of our tertiary medical center may possibly explain the higher mortality rate observed. Some other studies have found mortality rate higher than that reported here (12,14,16,30,33).

It is interesting that lower trochanter BMD values were more significantly associated with death than were lower femoral BMD measurements. QUS measurements taken at baseline were also associated with higher risk of death and new fracture 5 years later. Our findings demonstrating significant association between QUS measurements and risk of new fractures are in agreement with previous reports (2,3,20). These results also reinforce the notion that QUS measurements could also be used to predict osteoporotic fracture and risk of death in the elderly population.

Recently, Samelson and colleagues (15) demonstrated a significant relationship between metacarpal BMD and the incidence of coronary disease in a prospective cohort. Our data demonstrated a significant association between fracture, low femur BMD and SI values, and higher cardiovascular mortality. These epidemiological results may suggest potential interrelation between bone biology and vascular pathology, a topic that has received increasing interest in current literature (11,14,15,18,20).

Interesting evidence from basic studies on osteogenesis and angiogenesis can provide potential biological reasons that explain the epidemiological association between osteoporosis and atherosclerosis as described in this article (21,22,25,26). Expression of several osteoblast-specific marker genes has been described in atherosclerotic lesions and suggests that vascular cells differentiate and acquire an osteoblast phenotype (34,35). Moreover, the microenvironment rich in nitric oxide increases cellular differentiation from endothelial cells to osteoblast-like or calcificant vascular cells, which in turn initiate posterior mineral deposition in the atheroma plaque. It is interesting that low-density lipoprotein-oxidized, a main product involved in the atherosclerotic pathophysiology, increases transdifferentiation of vascular cells into calcificant vascular cells and decreases differentiation of osteoblasts from bone marrow precursors (24,25,35,36). Unfortunately, biochemical bone

<table>
<thead>
<tr>
<th>BMD</th>
<th>New Fracture (HR [95% CI])</th>
<th>Death (HR [95% CI])</th>
<th>Cardiovascular Death (HR [95% CI])</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measurements (p Value)</td>
<td>(p Value)</td>
<td>(p Value)</td>
<td></td>
</tr>
<tr>
<td>Spine BMD</td>
<td>1.506 (0.947, 2.397)</td>
<td>1.313 (0.853, 2.020)</td>
<td>1.396 (0.803, 2.425)</td>
</tr>
<tr>
<td>Femoral neck BMD</td>
<td>2.009 (1.267, 3.184)</td>
<td>1.438 (1.061, 2.221)</td>
<td>1.284 (1.079, 2.262)</td>
</tr>
<tr>
<td>Trochanter BMD</td>
<td>1.621 (1.085, 2.424)</td>
<td>1.593 (1.072, 2.365)</td>
<td>1.305 (1.080, 2.184)</td>
</tr>
<tr>
<td>Stiffness index</td>
<td>2.233 (1.032, 3.828)</td>
<td>1.575 (1.105, 2.467)</td>
<td>1.544 (1.085, 2.795)</td>
</tr>
</tbody>
</table>

Table 3. Area Under the Curve Receiver Operating Characteristic (AUC ROC), Cutoff Point, Sensitivity (S), Specificity (E), and Positive and Negative Predictive Value (PPV and NPV) for Bone Mineral Density (BMD) Measurements, According to New Osteoporotic Fracture at Any Site in Brazilian Elderly Women

<table>
<thead>
<tr>
<th>BMD</th>
<th>AUC ROC</th>
<th>95% CI</th>
<th>Cutoff (%)</th>
<th>S (%)</th>
<th>E (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spine BMD</td>
<td>0.739</td>
<td>(0.659, 0.819)</td>
<td>0.870</td>
<td>71.4</td>
<td>63.3</td>
<td>32.6</td>
<td>89.9</td>
</tr>
<tr>
<td>Femoral neck BMD</td>
<td>0.773</td>
<td>(0.698, 0.847)</td>
<td>0.714</td>
<td>71.4</td>
<td>66.9</td>
<td>34.9</td>
<td>90.4</td>
</tr>
<tr>
<td>Trochanter BMD</td>
<td>0.772</td>
<td>(0.703, 0.842)</td>
<td>0.590</td>
<td>73.8</td>
<td>73.4</td>
<td>40.8</td>
<td>91.9</td>
</tr>
<tr>
<td>BUA</td>
<td>0.780</td>
<td>(0.697, 0.843)</td>
<td>100</td>
<td>73.8</td>
<td>67.5</td>
<td>36</td>
<td>91.2</td>
</tr>
<tr>
<td>SOS</td>
<td>0.757</td>
<td>(0.678, 0.836)</td>
<td>1504</td>
<td>71.4</td>
<td>69.8</td>
<td>37</td>
<td>90.8</td>
</tr>
<tr>
<td>Stiffness index</td>
<td>0.783</td>
<td>(0.709, 0.856)</td>
<td>67</td>
<td>71.4</td>
<td>72.2</td>
<td>39</td>
<td>91</td>
</tr>
</tbody>
</table>

Notes: BMD = measured in g/cm²; BUA = broadband ultrasound attenuation (dB/MHz); SOS = speed of sound (m/s).
turnover markers and cholesterol serum levels were not assessed in the present study.

Calcification of the abdominal aorta, longitudinal ligament, and intervertebral disc is an important limitation of spine BMD measurements to assess fracture risk in elderly patients. Accordingly, spine BMD measurements were associated with neither fracture risk nor mortality in our study. However, calcified lesions of the abdominal aorta are associated with greater bone loss, higher risk of fracture, and cardiovascular mortality (21,22). This aspect has not been explored in the present work, but it is important to keep the association in mind and evaluate atherosclerosis risk factors in patients with osteoporosis.

The use of several medications for cardiovascular diseases—statins (37), nitrates (38) and β-blockers (39)—has been associated with higher BMD and reduction of osteoporotic fracture risk. In our study, the association observed between low BMD and cardiovascular mortality was unexpected, and the use of these drugs was not investigated appropriately. Some other experimental studies have demonstrated significant reduction of atherosclerotic risk in bisphosphonate users (40).

Summary
We have found that low BMD and QUS measurements are associated with increased risk of future fracture and higher mortality rate due to cardiovascular disease. The results of our study suggest that combined strategies may be needed in the near future to improve health in the elderly population. It is also clear that there is a need for further epidemiological studies including men and individuals with previous atherosclerotic events to corroborate the association between low BMD and cardiovascular mortality. Other important unanswered question will be defining the role of calcium supplementation on vascular calcification in the elderly population and developing potential common therapeutic targets involving osteoporosis and atherosclerosis. Future epidemiological studies and clinical trials will be necessary to address whether the reduction of fracture risk, either by pharmacological or educational measures, can also impact mortality.

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