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Ultrasound Attenuation of the Calcaneus: A Sensitive and Specific Discriminator of Osteopenia in Postmenopausal Women

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Summary. Recent studies have evaluated techniques for estimating bone mass without radiation. The present study compares broadband ultrasound attenuation of the calcaneus and bone densities of the femoral neck and the lumbar spine in 17 normal women and 41 women with osteoporosis. Twenty of the osteoporotic women had spine (n = 16) or femoral neck (n = 4) fractures. There was a significant decrease in the broadband ultrasound attenuation ($P < 0.001$) in women with osteoporosis compared with normal women. The osteoporotic women also showed a decrease in vertebral ($P < 0.0001$) and femoral neck ($P < 0.0001$) densities compared with normal women. At 63 dB/MHz, the sensitivity and specificity of broadband ultrasound attenuation for decreased bone mineral density with or without fractures were 76%. All women with fractures had a broadband ultrasound attenuation less than 72 dB/MHz. This corresponded to a specificity of 41%. To determine whether broadband ultrasound attenuation correlated with trabecular bone volume, samples of cadaver calcaneus were analyzed. The histologic determination showed a significant correlation between broadband ultrasound attenuation and trabecular bone volume (r = 0.992, P = 0.008). These results suggest broadband ultrasound attenuation of the calcaneus reflects bone mass and can be used as a safe and sensitive indicator for decreased axial bone density.

Key words: Bone density — Ultrasound — Osteoporosis.

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Osteoporosis and osteoporotic fractures will affect an increasing number of our aged population. Current costs associated with the disease are estimated to be above $6.1 billion per year [1, 2]. Of the 1.2 million fractures attributed to osteoporosis annually, 227000 are hip fractures, which have been estimated to cause a 12–20% increase in mortality compared with age-matched controls [3]. Since fracture incidence varies inversely with bone mineral density (BMD) [4], a variety of techniques have been developed to quantify bone density. These techniques vary not only in the source of energy, but also in the site and type of bone measured. Single photon absorptiometry (SPA), which measures trabecular and cortical bone combined, is most often used to measure the density of the radius or the calcaneus. Dual photon absorptiometry (DPA) using ^{153}Gd, or more recently an X-ray source, and quantitative computed tomography (QCT) can be used to measure both the spine and the femur. QCT has the advantage of determining only the trabecular portion of the spine, but has the disadvantage of a significant exposure to radiation.

Ultrasound has also been used to study the properties of bone in vitro and in vivo. Langton et al. reported a technique using broadband attenuation of ultrasound to predict density [5]. They suggested the technique is sensitive to internal architecture. We have previously reported broadband ultrasound attenuation (BUA) of the calcaneus is a predictor of axial osteoporosis determined by DPA, demonstrating that the technique is both sensitive and specific [6]. The speed of sound through the patella has also been shown to differentiate normal and osteoporotic women [7].

The present study compares the BUA of the calcaneus determined by a new ultrasonic scanning technique with spinal and femoral neck bone densities determined by X-ray-based densitometry, in normal women, osteoporotic women, and women with osteoporotic fractures. Sensitivities and specificities for the range of BUA were calculated and compared with values for DPA and QCT. The BUA was also compared with the trabecular bone volume (TBV) of anatomic specimens to attempt to determine the correlation of the measurement with a histologic measure of bone mass.

Materials and Methods

Experimental Subjects

After obtaining approval of the Committee on the Protection of Human Subjects in Research of the University of Massachusetts Medical Center, and informed consent from the subjects, bone density of the hip and spine and BUA of the calcaneus were determined in 58 Caucasian women aged 58.1 ± 1.3 years (mean ± SEM; range 40–80 years) who were referred to one of the investigators (D.T.B.) for evaluation of possible osteoporosis. Seventeen women were defined as normal (aged 55.7 ± 2.2 years, range 42–80 years) by having normal vertebral and femoral neck bone density and no history of osteoporosis or fractures. Values were compared with 21 women (aged 54.0 ± 1.9 years, range 40–72 years) with osteoporosis, defined by a vertebral or femoral neck density greater than 1 SD below age-matched normals and no history of fractures. A third group of 20 women (aged 64.6 ± 2.1 years, range 42–79 years, $P < 0.007$) had history and radiologic evidence of vertebral or hip fractures without history of significant trauma. None of the women were on medications known to affect bone metabolism.

The normal women (aged 55.7 ± 2.2 years) were not significantly younger than women with osteoporosis (aged 59.2 ± 1.6 years). Of the women with osteoporosis, the women with fractures (aged 64.6 ± 2.1 years) were significantly older than women without fractures (aged 54.0 ± 1.9 years, $P < 0.001$). There was no significant difference in age between the 16 women with vertebral fractures and the 4 women with femoral fractures (64.5 ± 2.4 years vs. 65.2 ± 4.9 years).

Bone Density Measurement

Vertebral and femoral neck densities were determined by a dual-energy X-ray bone densitometer (Lunar DPX, Lunar, Madison, WI) [8]. The patients were studied at their convenience during an 8-month period.

BUA values were determined using an Ultrasonic Bone Analyzer (UBA) Model 575X (Walker Sonix, Worcester, MA). This system incorporates two transducers (emitting and receiving) in a water bath. The transducers scan around the region of interest in a trapezoidal matrix pattern. This corrects for positional variations in the anatomical structure of the calcaneus in different individuals. A reference measurement was made by acquiring a number of measurements at different frequencies (0.2 to 0.6 MHz) without the heel in the water bath. This resulted in a reference spectrum of transmitted energy versus frequency, which was stored in the memory of a microcomputer. The same measurement was repeated after positioning the heel between the transducers. A comparison of this ultrasonic spectrum with the reference spectrum produced the net attenuation spectrum from the heel.

Table 1. Broadband ultrasound attenuation (BUA) values in five women having repeated measures

Patient	BUA value (dB/MHz) 1	2	3	4	Coefficient of variation
1	47.6	52.7	51.6	52.3	3.3
2	69.2	67.3	69.8	70.0	1.3
3	70.6	73.2	71.0	70.7	1.3
4	54.4	52.1	58.1	54.9	3.0
5	93.0	89.1	87.3	—	2.4
Mean ± SD					2.3 ± 0.9

The calcaneus, like all materials, acted as a frequency-selective filter for the ultrasound beam, with the higher frequencies attenuated more than the lower frequencies. The attenuation was approximately a linear function of frequency and a curve was computed by linear regression. The slope of this curve was expressed in units of dB/MHz, and is referred to as the BUA value. Since the BUA was calculated in several areas, an averaging algorithm was used to obtain the reported BUA value. The reproducibility of the BUA measurement was determined in five women, each of whom had three or four separate measurements (Table 1). The coefficient of variation in these women was 2.3%.

To determine whether BUA correlated with bone histology, four fresh, unfrozen anatomic specimens (from cadavers, aged 69.2 ± 2.4 years, range 63–74 years, at death) were obtained from the University of Massachusetts Pathology Department. They were stored at 4°C prior to use (47.2 ± 8.7 days, range 20–60 days). The BUA of the specimen was determined as described earlier. Within 24 h of BUA determination, a sample was obtained, using a Creig biopsy needle, from the posterior portion of the calcaneus, the area of BUA measurement. The specimen was prepared for routine paraffin histology and stained with hematoxylin-eosin stain. The TBV was evaluated using histomorphometric techniques [9]. The investigator (S.M.) evaluating the histology was blinded to other data.

Analysis of Data

The difference between groups was evaluated using a two-tailed Student's *t* test. Correlations between values were tested by linear regression. To assess BUA of the calcaneus as a predictor of axial osteopenia, the sensitivity and specificity were calculated throughout the range of BUA values. Subjects with osteoporosis with or without fractures were designated "with disease," and subjects with normal bone densities and without history of back pain or fractures were designated "normal." A ROC curve [10] was plotted to determine how well BUA discriminated between normal and diseased populations. The area under the curve was calculated for comparison with other methods. All values are reported as mean ± SEM.

Results

The vertebral density was significantly higher in

Table 2. Bone density of the spine and femoral neck and ultrasound attenuation of the calcaneus in normal women and osteoporotic women with and without fracture

	Normal (n = 17)	Osteoporotic: All osteoporotic (n = 41)	No fracture (n = 21)	All fracture (n = 20)	Vertebral fracture (n = 16)	Hip fracture (n = 4)
Spine (L2–L4)	1.14	0.87*	0.90**	0.84**	0.84**	0.83***
(g/cm^2)	±0.03	±0.03	±0.03	±0.05	±0.06	±0.10
Femoral neck	0.83	0.63*	0.66**	0.61**	0.63**	0.53***
(g/cm^2)	±0.02	±0.02	±0.01	±0.03	±0.03	±0.07
Calcaneus	70.2	53.7**	56.3**	50.9**	52.9**	43.0***
(dB/MHz)	±2.9	±2.1	±3.2	±2.7	±2.9	±6.0

*, $P < 0.0001$; **, $P < 0.001$; ***, $P < 0.01$, all significantly different from normals

normal women (1.14 ± 0.03 g/cm^2) than in women with osteoporosis (0.87 ± 0.03 g/cm^2, $P < 0.0001$). There was no difference in vertebral density in osteoporotic women with or without fractures (0.84 ± 0.05 g/cm^2 vs 0.90 ± 0.03 g/cm^2) or in women with vertebral or femoral neck fractures (0.84 ± 0.06 g/cm^2 vs 0.83 ± 0.10 g/cm^2; Table 2). The femoral neck density was significantly higher in the normal women (0.83 ± 0.02 g/cm^2) than in the osteoporotic women (0.63 ± 0.02 g/cm^2, $P < 0.0001$). There was no difference in the femoral neck density between osteoporotic women with or without fractures (0.61 ± 0.03 g/cm^2 vs 0.66 ± 0.01 g/cm^2). The women with femoral fractures had lower femoral neck densities than women with vertebral fractures (0.53 ± 0.07 g/cm^2 vs 0.63 ± 0.03 g/cm^2, $P < 0.18$), but the difference was not statistically significant (Table 2).

The BUA values were significantly higher in the normal women (70.2 ± 2.9 dB/MHz) than in the osteoporotic women (53.7 ± 2.1 dB/MHz, $P < 0.001$). The osteoporotic women with fractures had a lower BUA than women without fractures (50.9 ± 2.7 dB/MHz vs 56.3 ± 3.2 dB/MHz), but this was not significant. Likewise, the BUA of women with femoral neck fractures was lower than women with vertebral fractures (43.0 ± 6.0 dB/MHz vs 52.9 ± 2.9 dB/MHz, $P < 0.10$), but the difference was not statistically significant (Table 2).

For all 58 women, there was a significant negative correlation between BUA and age ($r = -0.448$, $P < 0.001$), and a positive correlation between BUA and vertebral density ($r = 0.606$, $P < 0.0001$) and between BUA and femoral neck density ($r = 0.684$, $P < 0.0001$).

The sensitivities and specificities over the range of BUA measurements are shown in Fig. 1. At a BUA of 63 dB/MHz, the sensitivity and specificity for decreased BMD were 76%. At a BUA of 72 dB/MHz the sensitivity was 93% and the specificity 41%, but the sensitivity for fractures was 100%.

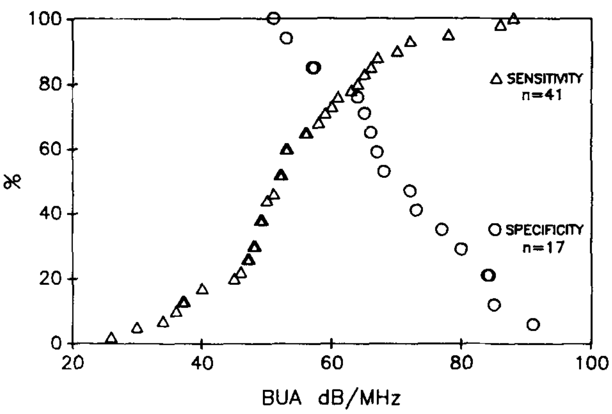

Fig. 1. Sensitivity and specificity of broadband ultrasound attenuation (BUA) of the calcaneus as a predictor of osteoporosis. Range of attenuation in women with osteoporosis (*triangles*) is compared with the range in women with normal spine and hip densities (*circles*). Four of the darkened triangles represent three patients, and three of the darkened triangles represent two patients.

Figure 2 shows the ROC curves (plotting sensitivity vs specificity for BUA) for the 41 women with osteoporosis and the 20 osteoporotic women with fractures. The area under the curve for the women with osteoporosis was 0.84.

In the anatomic specimens, there was a significant positive correlation between the BUA (50.8 ± 6.3 dB/MHz, range 68.9–39.6 dB/MHz) and TBV (13.6 ± 3.8%, range 24.0–6.0%, $r = 0.992$, $P = 0.008$), as shown in Fig. 3.

Discussion

The present study shows a significant decrease in the BUA of the calcaneus in women with decreased axial BMD and in women with osteoporotic fractures compared with normal women. The decrease

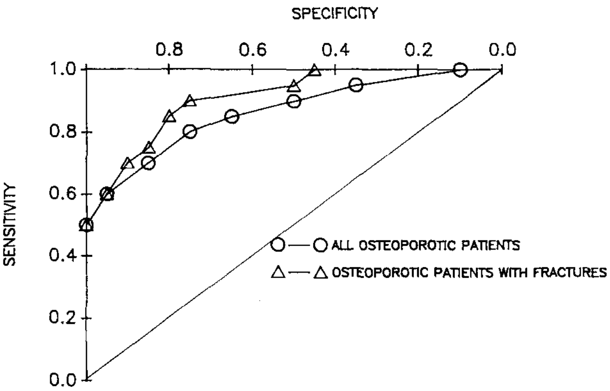

Fig. 2. ROC curves for women with osteoporosis. The two curves represent all 41 patients (*circles*) and the 20 patients with fractures (*triangles*).

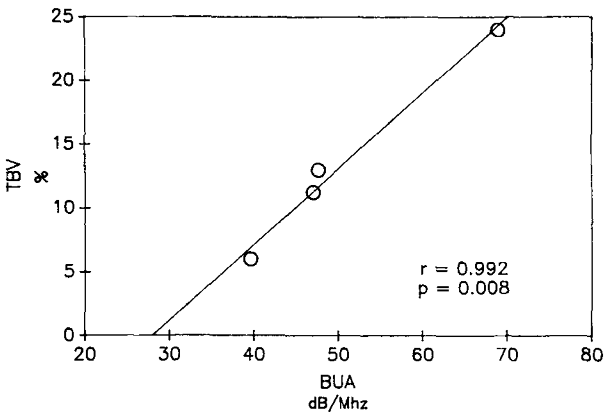

Fig. 3. Correlation between broadband ultrasound attenuation (BUA) and trabecular bone volume (TBV) of the calcaneus in anatomic specimens.

in BUA was 20% and 27% in the two groups, comparable to the decrease of 21% and 26% for both femoral neck and vertebral bone density measurements. Despite the significantly older age of the women with fractures, there was no significant difference in the vertebral or femoral neck density measurements or BUA value of osteoporotic women with or without fractures.

The precise pathogenesis of osteoporosis is still unknown. Recent studies suggest two independent but parallel processes [11]. The rapid decrease in bone content seen immediately after menopause is associated with a marked decrease in trabecular bone. This is superimposed on the age-related loss of bone, which shows a more gradual decrease in both trabecular and cortical bone. Weinstein and Hutson showed that 67.6% of the cancellous bone loss is due to an increase in the spacing of trabecular plates, while 23.2% is due to a decrease in plate width [12]. Other authors have found a high correlation between bone strength and the number and spatial relationship of the trabecular plates [13, 14]. Since these changes may occur up to 15 years prior to cortical thinning [15] and may be irreversible [11], early assessment of cancellous bone is important for reduction of the morbidity and mortality associated with osteoporosis.

We found the ultrasound technique to have sensitivities and specificities comparable to QCT and DPA [16, 17]. In our study, the area under the ROC curve for women with osteoporosis was 0.84, which is comparable to values reported for SPA, DPA, and QCT [18]. Our data showed correlations similar to those published by Pocock et al. [16] for lumbar spine and femoral neck densities ($r = 0.76$), and those published by Ross et al. [19] for calcaneus SPA and lumbar spine DPA (L3-L4, $r = 0.70$). However, as stated by Ross et al., correlations are of limited value; it is the ability to predict outcome that is essential for a clinical test. In our study, at a BUA of 72 dB/MHz the sensitivity of the test for osteoporosis-related fractures was 100%, while still retaining a specificity of 41% (Fig. 1).

Parfitt et al. reported a significant correlation between TBV of iliac crest bone biopsy specimens and age [20]. Delmas et al. found a correlation of $r = 0.53$ ($P < 0.001$) between TBV of the iliac crest and DPA of the lumbar spine in women with untreated vertebral osteoporosis [21]. In the present study, we found BUA of the calcaneus to be highly correlated with TBV of the same bone. Since TBV is an index of trabecular bone mass, the data suggest that BUA may reflect this histologic feature.

Current research suggests that osteoporosis is a systemic disease and that the early changes occur disproportionately in trabecular bone. We have demonstrated that BUA of the calcaneus correlates well with axial BMD as well as histologic determination of TBV at the site of measurement. The technique has a sensitivity and specificity comparable to other measures and predictors of bone density, and has the advantage of being radiation free. Further investigation is warranted, but our data suggest ultrasound attenuation may become an important noninvasive technique to study and predict changes associated with osteoporosis.

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