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Original Article

Quantitative Ultrasound of the Heel: Correlation with Densitometric Measurements at Different Skeletal Sites

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Abstract. To assess the utility of quantitative ultrasound (QUS) of the heel for osteoporosis screening, we studied a group of 170 early postmenopausal women using both QUS of the heel and dual-energy X-ray absorptiometry (DXA) at the spine, hip, forearm, and whole body. On the basis of the linear regression results between QUS and DXA, a 95% bone mineral density (BMD) estimate confidence range was defined. Correlation coefficients between the QUS measurements and DXA ranged from 0.26 to 0.63. The confidence ranges for the estimated BMD based on a QUS measurement of the heel were large, such that an estimation of skeletal BMD at any of the DXA sites measured was not possible. For example, an estimate of the normative anteroposterior spine BMD (i.e. the *T*-score or the *Z*-score) based on a calcaneal ultrasound reading would have an error of ±1.9 standard deviations. Results for predicting the normative BMD of the other DXA regions were similar, with expected errors ranging from ±1.4 to ±2.0 standard deviations. We therefore conclude that QUS is not suited for the screening of early postmenopausal women for low axial or peripheral BMD. However, QUS may have a role as an independent predictor of fracture by measuring skeletal properties in addition to bone density.

Keywords: Bone density; DXA; Osteoporosis; Ultrasound

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Introduction

Quantitative ultrasound (QUS) has been used for many years to investigate the mechanical properties of various engineering materials. Recently several commercial ultrasound devices have been introduced for investigating the material properties of bone tissue. These devices are designed to measure both the transmission velocity (speed of sound, SOS) and attenuation of ultrasound (broadband ultrasound attenuation, BUA) in the heel without the use of ionizing radiation. In a research setting, ultrasound reflection has also been investigated as a means for the non-invasive determination of the mechanical properties of bone [1]. Proponents claim that QUS has the potential to be an inexpensive screening tool for the evaluation of osteoporosis. Indeed several studies have shown the ability of QUS to distinguish accurately between normal subjects and patients with existing osteoporosis [2–5]. In addition, researchers have hypothesized that the ultrasonic properties of bone may be reflective of the trabecular microstructure, providing a non-invasive measure of bone quality [6–9].

At least one study has shown a QUS measurement of the heel to be predictive of hip fracture [10]. Additional studies have demonstrated that the ultrasonic properties of the heel increase in response to physical exercise and may be a useful monitor of skeletal response to physical therapy [11]. Reflection ultrasound measurements, slightly different from the transmission ultrasound techniques most commonly used, have been demonstrated to respond to fluoride intervention, suggesting the use of QUS for the evaluation and monitoring of pharmacologic intervention [12,13]. However, additional research is required to confirm the use of QUS for

fracture prediction and its utility for the monitoring of skeletal response to therapy or disease.

The potential use of QUS in a clinical setting rests on its ability to either (1) provide an inexpensive, non-radiation-based screening tool for the evaluation of bone density or (2) allow non-invasive determination of bone microstructure to enhance the evaluation of fracture risk beyond that obtainable from a density measurement alone. These two potential uses are dichotomous, in that the first demands a high correlation with conventional densitometric measurements, while the second requires that QUS provide information different from that available from densitometry. Several different researchers have studied the association between QUS and conventional densitometric measurements of the forearm [5,14,15], spine [2–5,15–17], hip [2–4,15–17] and heel [7,8]. The results from these studies have been varied, such that it remains unclear whether a QUS measurement is simply a surrogate for bone densitometry, or whether the future of the technique depends on its ability to provide structural information or enhanced fracture prediction.

In this study, the aim was to determine the association between transmission QUS and dual-energy X-ray absorptiometry (DXA) by performing measurements at all the clinically available measurement sites, specifically the lumbar spine (in both anteroposterior and lateral projections), the proximal femur, the radius, and the whole body. We have limited our study to women in the early postmenopausal period, the time when screening measurements of bone density would be of greatest benefit for therapeutic prevention. From these data, we wish to answer the question of whether QUS can provide an accurate tool for the clinical screening of potentially osteoporotic patients by providing reasonably accurate information about the bone mineral density of other skeletal sites.

Methods

A total of 170 healthy, postmenopausal women aged 44–59 years (mean 53.1±3.6 years) were studied. All women had ceased menstruating at least 6 months prior to measurement. None of the women were taking hormone replacements, and none had evidence of osteoporotic fracture as determined by lateral radiographs of the spine. Each subject gave informed consent according to the requirements of our institutional review board. Women were required to change into surgical clothes to avoid inclusion of artifacts in the densitometric measurements. All measurements were performed on the same day during a single visit.

The QUS measurements for this study were performed on a Lunar Achilles ultrasound unit (Lunar Corporation, Madison, WI). The right heel was scanned for all subjects using the manufacturer-recommended procedures as detailed in the operations manual. The Achilles measures both BUA and SOS simultaneously at the calcaneus and also provides a normative value called 'stiffness' (not to be confused with the engineering term of the same name as defined by materials scientists). 'Stiffness', as defined by the manufacturer, is a combined measurement of BUA and SOS expressed as a percentage of the young normal value. The precision error, defined as the standard deviation for a group of repeat measurements, was determined by performing a sequence of 26 QUS scans of a young healthy volunteer over a 4-week period. The standard deviation was 2.0 dB/MHz for the BUA measurement (1.8%), 8.31 m/s for the SOS measurement (0.5%), and 2.14% for 'stiffness'.

DXA measurements were performed with a Hologic QDR-2000 scanner (Hologic Inc., Waltham, MA). Anteroposterior (AP) spine, lateral spine, proximal femur, and total body scans were obtained in the standard array mode, while the forearm scan was obtained in single beam mode as an array mode does not exist for this measurement site. The bone mineral density (BMD, in g/cm^2) was recorded for each measurement site. An additional measurement of the estimated volumetric density of the spine was also calculated during the analysis from the paired AP and lateral spine measurements. Precision of the DXA measurements in our laboratory is 0.87% for the AP spine measurement and 1.73% for the femoral neck.

The association between the QUS parameters and the various DXA measurements was determined by the calculation of Pearson correlation coefficients. Significant correlations were defined as those with $p<0.05$. Linear regression parameters were also determined relating the QUS and DXA values, including the standard error of the estimate (SEE) for the regression equation. The SEE provides a measurement of the spread about the regression line, which in turn specifies the expected error when attempting to estimate one reading based upon another.

On the basis of the SEE of the linear regression, we have defined a confidence interval for use when estimating the DXA values from the QUS measurements as ±2 (SEE). Statistically, 95% of the 'true' DXA readings should fall within 2 SEE of the value as estimated by the linear regression. For example, if we measure the BUA of the heel and, on the basis of known regression relationships with DXA, attempt to estimate the total body BMD, our estimate should fall within 2 SEE of the actual total body BMD 95 times out of 100. From the regression relationships calculated from this study, we can calculate upper and lower confidence limits for the expected bone density at each skeletal site for a given QUS measurement:

$$\text{Upper BMD 95\% confidence limit} = [m(\text{QUS}) + b] + 2(\text{SEE}) \quad (1)$$

$$\text{Lower BMD 95\% confidence limit} = [m(\text{QUS}) + b] - 2(\text{SEE}) \quad (2)$$

where m is the slope of the regression line, QUS the ultrasound measurement (BUA, SOS, or 'stiffness'), b the intercept of the regression line, and SEE the standard error of the estimate for the regression.

The 95% confidence range for the predicted BMD value will be the difference between the upper and lower confidence limits defined by equations (1) and (2), which is simply 4 times the standard error of the estimate:

$$\text{BMD 95\% confidence range} = 4(\text{SEE}) \quad (3)$$

We can also define a normalized range for both the expected age-matched BMD (Z-score) and the young normal BMD (T-score) by dividing the confidence limit range calculated in equation (3) by the standard deviation of the normative data provided with the Hologic scanner for each DXA measurement site:

$$\text{Normalized 95\% BMD range} = \frac{4(\text{SEE})}{\text{SD}} \quad (4)$$

where SD is the standard deviation of the normative DXA data at the skeletal site to be estimated.

As the Z- and T-scores are used primarily when evaluating skeletal status, the size of this normalized 95% BMD range will be an indicator of the usefulness of a calcaneal QUS measurement for the assessment of BMD in early postmenopausal women at different skeletal sites.

If QUS is to be useful for screening of women in order to identify those without need of further examination (such as a site-specific DXA measurement), the confidence in the QUS measurement must be such that the clinician is comfortable with declaring a woman to be 'normal' without the need for an additional DXA examination. From a theoretical standpoint, this requires that the confidence range defined by equation (3) be approximately equal to the standard deviation of the DXA measurement, such that confidence limits will not exceed the variation of the normative population. However, a more realistic goal is that the confidence range be no larger than twice the DXA standard deviation, allowing for some error in the QUS measurement. For this investigation, we have defined an acceptable normalized BMD confidence limit as equal to 2.0 or less, which from equation (3) would require the SEE to be no larger than one-half the standard deviation of the DXA normative data.

Results

Table 1 presents the correlation coefficients between the QUS and DXA measurements on the 170 women of the study. In general the correlations were poor, ranging from 0.26 to 0.63. The direct correlation between BUA and SOS was low ($r = 0.55$), while the 'stiffness', which is a combination of the BUA and SOS values, revealed high correlations with both the BUA and SOS as expected.

The results of the linear regression analysis (slope, intercept, and SEE) are shown in Tables 2, 3, and 4 for BUA, SOS, and 'stiffness', respectively. Representative scatter plots of BUA and SOS are shown in Figs. 1 and 2, showing the most common DXA measurements,

Table 1. Correlation coefficients between quantitative ultrasound (QUS) and dual-energy X-ray absorptiometry (DXA) measurements

	BUA	SOS	'Stiffness'
BUA	1.000		
SOS	0.552	1.000	
'Stiffness'	0.802	0.907	1.000
Anteroposterior spine	0.461	0.486	0.545
Lateral spine	0.382	0.491	0.510
Volumetric spine	0.257	0.456	0.431
Femoral neck	0.417	0.501	0.551
Trochanter	0.402	0.490	0.520
Intertrochanteric	0.451	0.522	0.567
Ward's triangle	0.330	0.480	0.483
Total hip	0.453	0.525	0.571
1/3 radius	0.294	0.333	0.372
Ultradistal radius	0.365	0.511	0.512
Whole body	0.509	0.570	0.626

BUA, broadband ultrasound attenuation; SOS, speed of sound measurement (both at the heel).

Table 2. Linear regression parameters for dual-energy X-ray absorptiometry (DXA) v the calcaneal broadbend ultrasound attenuation (BUA)

DXA measurement site	Slope	Intercept	Standard error (SEE)
Anteroposterior spine	0.00491	0.370	0.107
Lateral spine	0.0304	0.322	0.0835
Volumetric spine	0.000505	0.138	0.0215
Femoral neck	0.00358	0.317	0.0885
Trochanter	0.00321	0.273	0.0829
Intertrochanteric	0.00566	0.357	0.127
Ward's triangle	0.00340	0.221	0.110
Total hip	0.00442	0.339	0.0987
1/3 radius	0.00133	0.499	0.0490
Ultradistal radius	0.00166	0.224	0.0481
Whole body	0.00375	0.612	0.0720

Table 3. Linear regression parameters for dual-energy X-ray absorptiometry (DXA) v the calcaneal speed of sound (SOS)

DXA measurement site	Slope	Intercept	Standard error (SEE)
Anteroposterior spine	0.00185	−1.91	0.106
Lateral spine	0.00140	−1.48	0.0787
Volumetric spine	0.000320	−0.296	0.0198
Femoral neck	0.00154	−1.64	0.0843
Trochanter	0.00140	−1.51	0.0790
Intertrochanteric	0.00235	−2.60	0.121
Ward's triangle	0.00177	−1.46	0.097
Total hip	0.00171	−2.12	0.102
1/3 radius	0.000539	−0.177	0.0483
Ultradistal radius	0.000834	−0.868	0.0444
Whole body	0.00151	−1.27	0.0687

Table 4. Linear regression parameters for dual-energy X-ray absorptiometry (DXA) v the calcaneal ultrasound parameter of 'stiffness'

DXA measurement site	Slope	Intercept	Standard error (SEE)
Anteroposterior spine	0.00466	0.529	0.101
Lateral spine	0.00326	0.387	0.0777
Volumetric spine	0.000678	0.137	0.0201
Femoral neck	0.00380	0.398	0.0813
Trochanter	0.00333	0.352	0.0774
Intertrochanteric	0.00572	0.510	0.117
Ward's triangle	0.00400	0.263	0.102
Total hip	0.00448	0.457	0.0909
1/3 radius	0.00135	0.534	0.0476
Ultradistal radius	0.00187	0.252	0.0443
Whole body	0.00371	0.720	0.0652

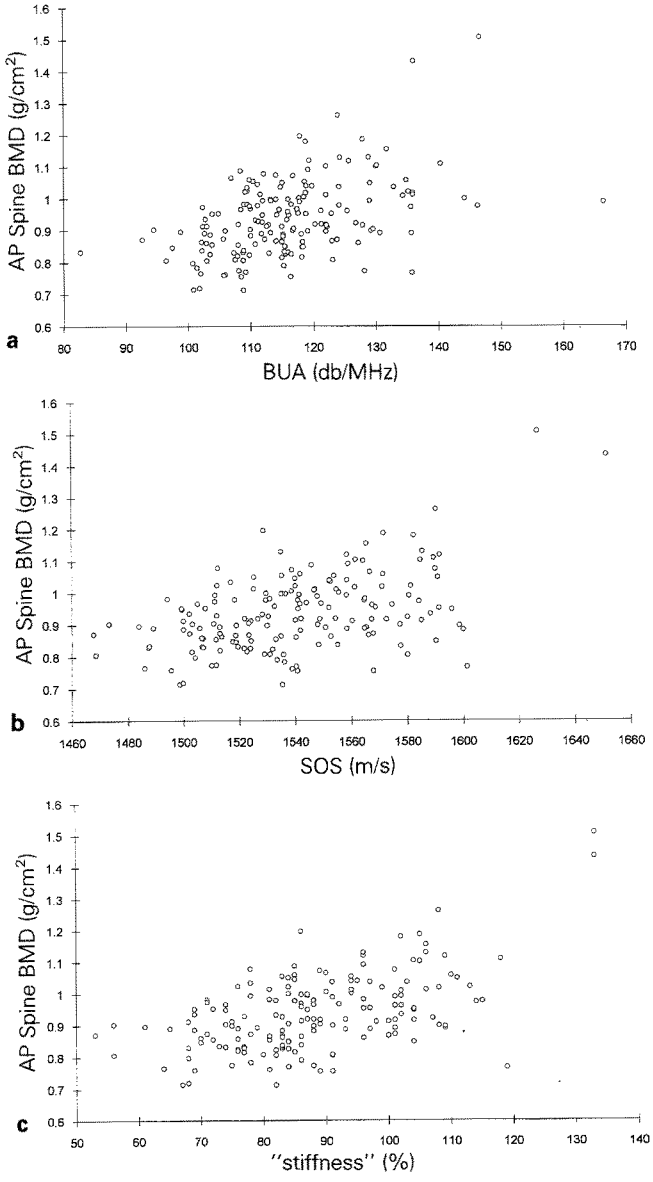

Fig. 1a–c. Scatter diagrams showing the measured anteroposterior (AP) spine bone mineral density (BMD) as a function of: **a** the broadband ultrasound attenuation (BUA), **b** the speed of sound (SOS), and **c** the 'stiffness' for the 170 women in the study.

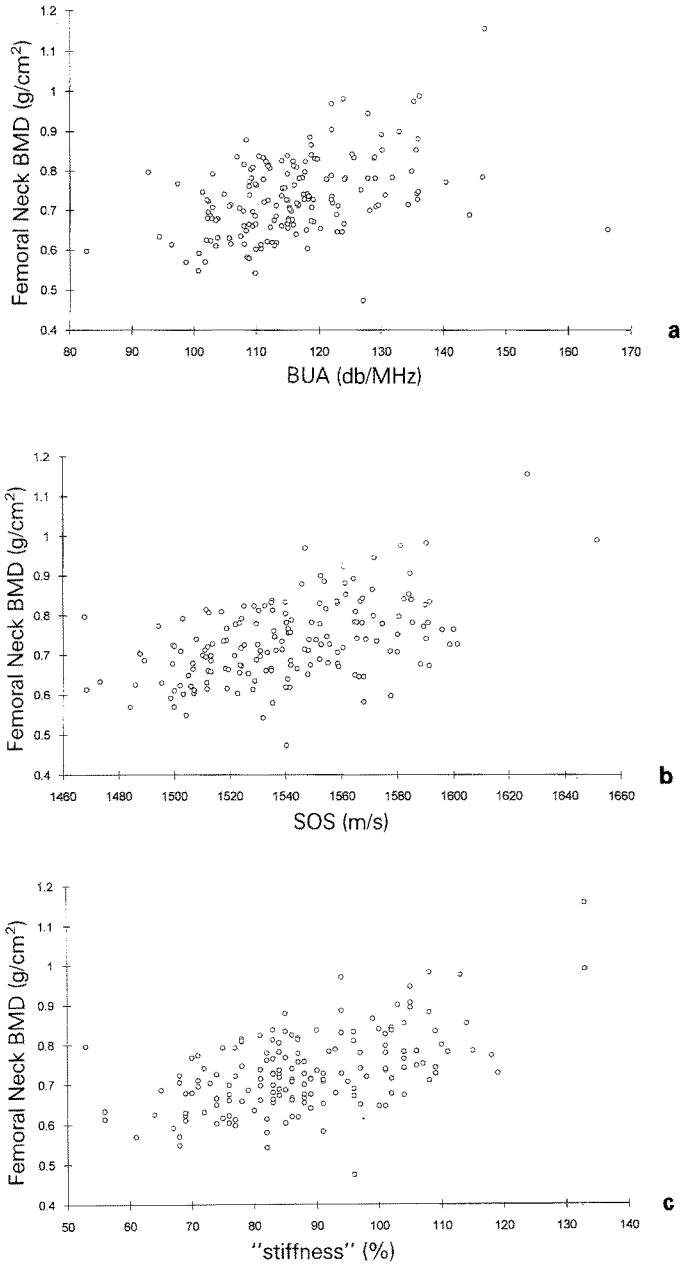

Fig. 2a–c. Scatter diagrams showing the measured femoral neck bone mineral density (BMD) as a function of: **a** the broadband ultrasound attenuation (BUA), **b** the speed of sound (SOS), and **c** the 'stiffness' for the 170 women in the study.

AP spine and femoral neck, as a function of the QUS values. As evidenced by these plots and the SEE values shown, the spread around the regression lines was large.

In Fig. 3, the predicted normalized BMD ranges are shown for the various DXA measurement sites. None of the confidence ranges were equal to or less than 2.0 due to the poor correlations and large SEE of the regression relationships. The ranges extend from 2.8 to 4.0 standard deviations for the different DXA sites studied. This range extends symmetrically to both sides of the estimated DXA value. Thus when attempting to estimate the age-matched or young normal normative bone density from a QUS measurement of the heel, the

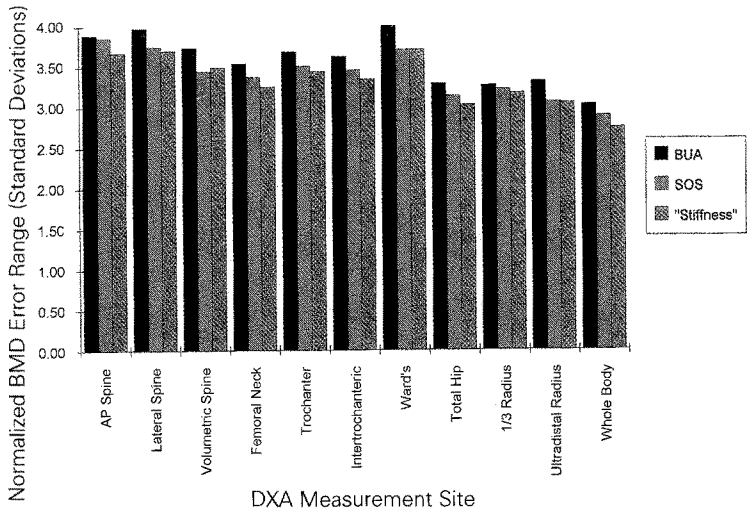

Fig. 3. The expected normalized bone mineral density (BMD) confidence range when attempting to predict the age-matched (Z-score) or young normal (T-score) values for the various dual-energy X-ray absorptiometry (DXA) measurement sites on the basis of a single quantitative ultrasound (QUS) measurement of the heel. BUA, broadband ultrasound attenuation; SOS, speed of sound. Values are determined from the linear regression relationships derived in this study as described in Methods. The confidence range extends symmetrically to both sides of the estimated DXA value. For example, at the anteroposterior (AP) spine, the expected error range is 3.9 standard deviations for BUA and SOS, such that the estimated Z- and T-scores at this site will have an error of ± 1.9 standard deviations.

resultant Z-score or T-score can be expected to be in error by ± 1.4 to ± 2 standard deviations, depending on the skeletal site.

Discussion

The use of QUS for assessing skeletal fragility has received significant attention in recent years. Several companies currently manufacture QUS units specifically designed for the evaluation of osteoporosis, though none of these units is yet approved for use in the United States. QUS has several potential advantages, including relatively low cost, no need for ionizing radiation, compact size, and ease of use. These advantages would make QUS an ideal screening tool if it can be shown to be an accurate indicator of skeletal density and fracture risk. In addition to the practical advantages, a measurement of ultrasonic properties should in theory be directly related to the material properties of bone, thus providing a non-invasive measurement of bone structure or quality beyond that obtainable from a density measurement alone.

Thus study has been designed to address the suitability of QUS as a screening tool for the estimation of BMD at various skeletal sites. We have chosen early postmenopausal women for the study, as this represents the population who would most directly benefit from a screening measurement. On the basis of the results we conclude that the relationships between QUS and DXA are too weak to allow accurate prediction of the BMD at any skeletal site from a QUS measurement of the heel. The associated error in the relationship between QUS and DXA is large enough that virtually no subjects can be deemed to have normal BMD at any skeletal site on the basis of a QUS measurement of the heel.

The correlation between QUS at the heel and BMD measured at a different skeletal sites will be influenced by both differences in the measurement site and differences in instrumentation. From previous densitometric studies using DXA [18,19] we know that BMD measurements at different skeletal sites in the same subjects will show at best moderate correlations (r=0.5–0.7). A check of the intercorrelations between the DXA measurements in this study confirms this result, with the correlation coefficients between the AP spine measurement and the BMD measured at femoral neck, ultradistal radius, and total body being 0.60, 0.55, and 0.82, respectively. Thus a portion of the observed discrepancy between QUS and DXA can be attributed to differences in the skeletal properties of the sites measured. However, in a recent report by Glüer et al [8], site-matched measurements of BUA and single photon absorptiometry at the calcaneus showed a correlation of 0.56 in a group of 33 subjects. When the analysis was limited to the 25 women included in the study, the correlation coefficient improved to 0.70. From these site-matched measurements of QUS and BMD it must be concluded that basic differences in the measurement technique itself appear to influence significantly the observed correlation between QUS and conventional bone densitometry. The results of the present study confirm this conclusion, accounting for the relatively low correlations observed in comparison with those seen using radiation-based densitometry alone.

Previous studies have shown correlations between calcaneal BUA and bone density at various skeletal sites ranging from 0.28 to 0.87 [2–5,14–17]. However, in several of these previous studies the age range of the subjects studied was considerable and in general included a number of elderly women 70 years and older. This study has been limited to women in the immediate

postmenopausal period, when changes in BMD are occurring at a relatively fast rate. Due to the differential rates with which the various skeletal sites respond to a decline in estrogen levels, it can be expected that the correlations between axial and peripheral measurements might be reduced in comparison with other groups where the rates of change are not as severe. In studies which were limited to perimenopausal women between 45 and 54 years of age, correlations between BUA and DXA were relatively poor, ranging from 0.28 to 0.40 [16,17]. The results of the present study confirm these earlier reports in perimenopausal women and also suggest that measurements of SOS and 'stiffness' cannot improve the relationship with BMD.

Though our results indicate that QUS has little value for the estimation of skeletal BMD as measured by DXA in early postmenopausal women, it does not address the issue of the utility of QUS for evaluating bone properties other than density. It is possible that QUS can provide additional information not included in a density measurement. This information might allow QUS to be equal or superior to bone density techniques for evaluating fracture risk. Large prospective fracture endpoint trials are needed to answer this important question. However, if QUS is to have a clinical use, it will be as an independent predictor of fracture and not as a screening tool to identify postmenopausal women with low axial or peripheral BMD.

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