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Osteoporosis detection in postmenopausal women using axial transmission multi-frequency bone ultrasonometer: clinical findings

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Abstract

The objective of this study was to evaluate if the Bone UltraSonic Scanner (BUSS) can detect osteoporosis in postmenopausal women. BUSS is an axial transmission multi-frequency ultrasonometer for acquisition of wave propagation profiles along the proximal anterior tibia. We derived 10 diagnostically significant BUSS parameters that were then compared with the DXA spine T-score, which was used in this study as the “gold standard” for the assessment of osteoporosis (T-score <−2.5). BUSS wave parameters were studied in 331 postmenopausal women examined by 9 trained operators at 3 clinical sites with use of 3 devices. The efficiency of each BUSS parameter in osteoporosis detection was assessed using a receiver operating characteristic curve analysis. Area under the curve (AUC) for each of 10 parameters ranged from 58.1% to 70.2%. Using these parameters a linear classifier was derived which provided at its output 83.0% AUC, 87.7% sensitivity and 63.2% specificity to DXA-identified osteoporosis. The results of this study confirm BUSS’s capability to detect osteoporosis in postmenopausal women.

Keywords

Bone quantitative ultrasound; multi-frequency; axial scanning; wave propagation parameters; osteoporosis; postmenopausal women

Introduction

Osteoporotic fractures are a serious public health problem. The increased risk of bone fracture related to osteoporosis results from decreasing bone mass, increasing porosity and thinning of bones. Low bone mineral density (BMD) as measured by dual-energy x-ray absorptiometry (DXA) is considered a strong predictor of fracture risk. Thus, DXA T-score

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of -2.5 or lower is considered the current “gold standard” in osteoporosis assessment [1, 2]. Meanwhile, low BMD only partly explains skeletal fragility [3]. For instance, increased fracture risk in type 2 diabetes patients is not usually associated with low BMD but may be more related to changes in bone quality that affect bone strength [4]. Macro- and micro-structural characteristics such as intracortical porosity and accumulation of microcracks are important aspects of “bone quality” that may be relevant [5].

Recent advances in ultrasonic techniques showed a high potential of quantitative ultrasound (QUS) to characterize the mechanical and structural properties of bone [6]. Currently, only heel QUS has proved to be comparable to DXA in predicting fracture risk [7, 8]. The heel QUS devices like Achilles Express (GE Lunar), Sahara (Hologic) or UBIS 5000 Ultrasound Bone Sonometer (DMS Group) have been marketed to complement radiological densitometry and to primarily satisfy the demand for mass osteoporosis assessment. However, the authors of a comprehensive review on accuracy of QUS for detection of osteoporosis concluded that “calcaneal quantitative ultrasound results at commonly used screening thresholds seem to be insufficient to rule out or rule in DXA-determined osteoporosis” [8].

Axial QUS devices for tibia and forearm targeting the cortical bone were also approved for use [9]. Tibial measurements of ultrasound velocity or “speed-of-sound” (SOS) demonstrated sensitivity to changes in the cortical compact bone associated with mineral metabolism in renal disease [10] and Crohn’s disease [11], however, not enough encouraging data related to evaluation of osteoporosis have been reported. During recent years, several novel technologies based on different physical principles targeting the cortical bone have been tested in human studies. Experimental study with the proximal femur through-transmission scanner showed potential to measure propagation parameters of guided waves in the cortical shell of the femoral neck with an ultrasound beam targeted to the bone through a bulk of the surrounding soft tissues [12]. Correlation of ultrasound propagation parameters with BMD in the distal radius was demonstrated by through transition measurements in the forearm at locations containing composition of soft tissues and bone [13]. Velocity of the fast arriving signal was measured in long bones by the surface transmission of ultrasound at 0.4 MHz frequency using a bidirectional probe with a linear array of transducers [14–16]. The results showed better correlation of the longitudinal wave velocity with the volumetric cortical BMD for the radius, where the ratio of cortical thickness to wavelength is lower than in the tibia. Data on backscattering from the femoral neck were obtained in vivo and showed difference between subjects with and without osteoporotic fracture [17]. In most of these studies, diagnostic capacity of a single measurement parameter was examined. No ultrasonic approach has been proposed where diagnostics is based on combination of multiple parameters reflecting versatile properties of the bone.

A novel Bone Ultrasonic Scanner (BUSS) developed at Artann Laboratories [18, 19] combines the use of guided and bulk waves in a broad frequency band from 60 kHz to 1200 kHz and analyzes topographical changes of the ultrasound propagation parameters from the epiphysis towards diaphysis of a long bone. Our earlier studies using a dual-frequency modality showed ability of the axial profiles along the medial surface in the proximal tibia at low and high frequencies to discriminate between stages of normal, osteopenic and osteoporosis determined by hip DXA [18]. The technology implemented in the initial design of BUSS has been significantly improved and modified enabling the device to radiate and receive a train of multiple impulses that generate various modes of acoustic waves. The details of the multi-frequency approach and a new version of the broadband BUSS device are described in our companion paper in this issue of *Ultrasonics* [20]. In this article, the results of a multi-parametric analysis of axial profiles in broadband frequency range

obtained by BUSS in a multisite clinical study are presented and clinical significance of these results is discussed.

Materials and Methods

Study Design and Protocol

The primary objective of the clinical study was to assess the capability of BUSS for osteoporosis detection (clinical trial identifiers: NCT01056432 and NCT01123421). The BUSS examination procedure is illustrated in Fig. 1. Several parameters (further called BUSS parameters) that characterize received acoustic waveforms along the tibia at different carrier frequencies were calculated from the recorded BUSS examination data and were used for characterization of bone quality. BUSS performance was compared to DXA data which was used as the "gold standard" for detection of osteoporosis. A non-blinded data analysis was used to evaluate diagnostic accuracy of BUSS vs DXA spine T-score.

The study was conducted at three investigational sites: Health Smart Medical Center (Philadelphia, PA), Mayo Clinic (Rochester, MN), and Catholic Health, Sisters of Charity Hospital (Buffalo, NY). The BUSS examinations were performed by trained study staff. The clinical protocol was approved by the Institutional Review Boards at each site. The study was conducted in compliance with the Health Insurance Portability and Accountability Act.

We studied postmenopausal women, age 50–90 years, of any race or ethnical group, and who did not have other metabolic bone disease. All women had DXA spine and hip examination completed at the same time or within one year prior to their BUSS examination. Study exclusion criteria were: open wounds, rashes or active skin infections at the tibial testing area; recent tibia surgery; abnormal tibia anatomy; body mass index (BMI) > 35.0 kg/m²; current or previous tibial fracture on side of testing; stroke with total or partial paralysis with residual disability lasting more than 3 months; teriparatide use currently or within the past 3 months, as well as drugs under research protocols, and unstudied or unapproved drugs. A hard copy of the Case Report Form with the clinical characteristics of all enrolled subjects was submitted for data review and analysis. The DXA data were collected with the use of the Delphi 70315 QDR series device (Hologic, Bedford, MA) with software QDR for Windows option at site 1; the Prodigy device (GE Medical Systems, Waukesha, WI) with software version 6.10.029 at site 2; Prodigy Lunar device (GE Medical Systems, Waukesha, WI) with encore software version 13.60 at site 3.

BUSS Device and Examination Procedure

BUSS is an axial transmission multi-frequency ultrasonometer for acquisition of wave propagation profiles along the proximal anterior tibia. Detailed description of the device has been previously reported [20]. Examination is conducted with the subject in the sitting or lying position. The hand-held ultrasonic probe is designed ergonomically for easy positioning. The probe includes a pair of wideband ultrasonic transducers and a preamplifier for the received ultrasonic signals. The design ensures acoustic isolation between the transducers, preventing ultrasonic signals from propagating directly between them through the probe. The acoustic base is fixed at 40 ± 0.1 mm. The excitation waveforms are short pulses with two sinusoidal periods under a Gaussian function envelope. BUSS transmits a train of 5 pulses with the following carrier frequencies: 60 kHz, 100 kHz, 400 kHz, 800 kHz, and 1200 kHz. The output voltage of the transmitter is 150 V peak-to-peak. The entire transmitted frame is comprised of 32,000 samples with a 33 MHz sampling rate. The optimal scan trajectory lies in the middle of the medial surface of the tibia, from the knee joint to the diaphysis. Scanning the tibia is performed by manually positioning the probe along the bone according to the marks on an acoustically transparent strip applicator

attached to the surface of subject's proximal and medial tibia. The applicator is lubricated on both sides by the ultrasonic gel for better transmission of ultrasound. BUSS records 15 sequential ultrasonic measurements with step of 1.0 cm along the subject's proximal tibia and acquires the ultrasonic propagation signals at 5 different frequencies for each measurement. System software provides an operator with on-screen cues about the adequate positioning of the probe based on the amplitude of received signal. Each measurement consists of positioning the probe at a specified location and holding the probe for several seconds to collect the ultrasound data. Once data is collected, the system signals the operator to move to the next measurement point. The overall scanning length is about 15 cm and the total duration of the procedure is under 5 minutes. Ultrasonic exposure level of BUSS is an order of magnitude lower than the FDA approved safety level for standard diagnostic ultrasonic equipment.

The identical devices were used at each of the three clinical sites. The devices were cross-tested at the component level before the final assembly and were validated by multiple measurements on a set of phantoms mimicking "healthy", "osteopenic", and "osteoporotic" bone conditions. Inter-device reproducibility ± 0.8 and inter-operator variability ± 1.2 of the Bone Quality Index (see below Eq. (3)) calculated as standard deviation was demonstrated.

Study Population

The BUSS clinical data set presented in this paper was collected and recorded between February 2010 to August 2012. Initially, after receiving written informed consent, 338 postmenopausal women were enrolled in the study at three different clinical sites. Seven women were excluded from the study and subsequent data analyses due to exceeding the BMI $> 35.0 \text{ kg/m}^2$ parameter. Summary of study subject enrollment and exclusion at each site is shown in Table 1. Collectively, there are 331 postmenopausal women included in the analyses (Table 1). There are 64 women from the first clinical site 1, 147 women from the second site (half of whom, by design, had a history of fractures involving the distal forearm or the thoracic or lumbar spine), and 120 women from the third site. The mean age ($\pm$ SD) of subjects was 64.2 ± 12.6 , 69.8 ± 9.7 and 65.9 ± 9.3 years for each clinical site, respectively.

DXA T-scores of the spine were used as the "gold standard" for determination of osteoporosis for data analysis. Table 1 describes the distribution of osteoporosis based on DXA derived T-scores among the 331 women who were analyzed. Overall, there were 155 women were classified as normal (DXA T-score > -1.0) and 111 women who were characterized as osteopenic ($-2.5 < \text{DXA T-score} < -1$), while 65 women were considered osteoporotic (DXA T-score < -2.5).

BUSS Parameters

Of the 30+ tested parameters related to ultrasonic wave propagation along the tibia we selected 10 with the area under ROC curve above 57% and analyzed them further for diagnostic significance in osteoporosis detection. A description of each of these parameters is provided in Table 2. The specific tibia zone used in application of each parameter is also shown in Table 2. These parameters can be subdivided into the following four categories: amplitudes of the received waves at different frequencies or their ratio (P1, P2, P6, P7, P8), waveform profiles along the tibia at different frequencies or affinity indexes (P4, P5), wave propagation speed or signal position in time (P3), and shift of wave pulse center frequency (P9). In addition, we included the subject's BMI (P10) as a parameter to be used in calculation of BUSS Bone Quality Index (BQI) as described in the next section.

The affinity index was obtained by comparing the acquired "wave profile" with an average wave profile calculated for subjects with DXA spine T-score < -2.5 (osteoporotic group)

and for the subjects with DXA spine T-score > 0.0 (referent normal group). The resulting “wave profile” is an image showing the signal amplitude on a 2-D plot, where the time is the first coordinate and the location along the tibia is the second coordinate. In this comparison we calculated a ratio of two differential convolutions: tested profile vs osteoporotic group and tested profile vs normal group. These calculations were completed with the signals normalized to their maximum amplitude.

The position of acquired signal S passed along the tibia in the time scale t was calculated as data sample index (i) for signal “center mass” according to the equation (1):

$$i = \frac{\sum_{t=start}^{end} [S(t)^2 * t]}{\sum_{t=start}^{end} S(t)^2} \quad (1)$$

We applied complex wavelets analysis with the use of continuous Gaussian transforms [21] to estimate a shift of wave center frequency in the signal passed along the tibia. Specifically, the frequency shift was calculated as a difference between the center frequency of acquired wave packet and the frequency of the emitted pulse. The center frequency was defined from the frequency-time domain for the wavelet modulus $Wm(f,t)$ calculated as:

$$Wm(f,t) = \sqrt{(wreal(f) * S)[t]^2 + (wimag(f) * S)[t]^2} \quad (2)$$

Where: f is the frequency; t is the time; $wreal(f)$ and $wimag(f)$ are real and imaginary wavelet transforms, respectively; S is the analyzed signal; symbol $*$ means a convolution.

Statistical Analysis

Assessment of the diagnostic significance of each parameter was completed with the aid of the statistical toolbox in MATLAB 6.1 (MathWorks, Natick, MA). The wavelet analysis was completed with the use of Builder C++ XE2 compiler (Embarcadero, San Francisco, CA). For visual evaluation of the analyzed clinical data distributions within the subjects groups, we used boxplots for data representation of each analyzed parameter and their combinations. In descriptive statistics, the boxplot is a convenient and widely accepted way of graphically depicting groups of numerical data or data samples [22]. Boxplots are able to visually show distinctions of data samples without making any assumptions of the underlying statistical distribution. The spacing between the different parts of the box helps to compare variance, to identify skew (asymmetry) and outliers (small circles). We have used the notched boxplot [23] showing a confidence interval for the median value. The intersection or divergence of confidence intervals for two subject samples is a visual analog of the paired t -test.

A correlation coefficient calculated by the standard procedure implemented in MATLAB software [24] was applied to analyze the strength and direction of the linear relationship between each of the ten calculated features. We calculated Pearson product-moment correlation coefficients, which are obtained by dividing the covariance of the two variables by the product of their standard deviations.

To compare diagnostic performance of each parameter in characterizing osteoporosis and to evaluate parameter combined effectiveness, we used the receiver operating characteristic (ROC) curve analysis [25]. The area under the curve (AUC) is determined from plotting the sensitivity (%) vs 100-specificity (%) of a test as the parameter threshold varies over its entire range of tested variable. The AUC is interpreted as the diagnostic accuracy, which is

the probability that the test will produce a value for a randomly chosen subject with osteoporosis that is greater than the value for a randomly chosen healthy subject [26]. An area of 100% indicates a perfect prediction; an area of 50% is a chance result.

Classifier

To combine the diagnostically significant parameters which differentiate subjects with osteoporosis, we employed a linear classifier. The performance (i.e., testing accuracy) of linear classifiers appeared to be similar to much more complex nonlinear classifiers such as kernel methods, but training with reference data and testing (processing) speed is much higher [27].

We calculated for each parameter its average value (P_i^a) and standard deviation (SD_i) for the analysed data sample. The Bone Quality Index (BQI) represents a linear combination of BUSS parameters minus the average and normalized on standard deviation to provide statistically equal contribution from each parameter into BQI :

$$BQI = \sum_{i=1}^{i=k} (P_i^m - P_i^a) / SD_i \quad (3)$$

where k is a number of parameters which contribute to BQI ; i is a serial number of the parameter; P_i^m is the measured (incoming) value of i -parameter to calculate BQI for that measurement (examination). The positive sign (+) of BQI will correspond to normal; the minus (−) will correspond to osteoporosis.

Results and Discussion

Table 3 presents our findings on the diagnostic performance of parameters P1–P10 in detecting osteoporosis in the 331 postmenopausal women studied. We used DXA spine T-score as the reference for classifying osteoporosis. The first line in Table 3 represents the diagnostic accuracy of the parameter, the second is the correlation coefficient (R) with DXA spine T-score, the third is the p-value and the last line is the t-test outcome for a null hypothesis. The value of h is equal one if the null hypothesis is rejected at the 0.05 significance level and equal zero otherwise. We found the area under ROC curve for a single parameter ranging from 58.1% to 70.2%. Seven parameters demonstrate AUC in the range from 60% to 70%. The best diagnostic accuracy of 70.2% demonstrates the signal amplitude for 60 kHz pulse (P1) measured in proximal zone of tibia with trabecular structure (Table 2). Parameter (P7), signal amplitude ratio 800/60 kHz, measured in tibia transition zone did not pass the test for the diagnostic significance having p-value of 0.096 which is above the pre-determined requirement of a $p < 0.05$; though this parameter has AUC = 60.2%. Parameter (P7) was also poorly correlated with the DXA data therefore it was excluded from BQI calculation. Parameter (P8) had a poor correlation, but since it passed t-test with p-value of 0.040 it was included in the linear classifier and contributed about 2.0% improvement in osteoporosis detection.

Table 4 presents pair correlation coefficients for BUSS parameters P1–P10. This table has symmetry relative to a diagonal, which is expressed by 1, given that each data set perfectly correlates to itself. We expected that correlated parameters with $R > 0.5$ would provide no improvement of the BQI . The calculated results confirmed these expectations; P2 and P5 give zero and even negative contribution to BQI . Thus, we excluded parameters P2 and P5 from participation in BQI calculation.

Comparative boxplots for the subjects with osteoporosis (65 women) vs women with osteopenia or normal BMD (266 women), as classified by DXA, are shown in Fig. 2. The central horizontal line inside each boxplot corresponds to the median value of the data distribution, as the confidence interval for the median is depicted by a notched beam range on each boxplot. Lower and upper horizontal lines of the box correspond to the first (25%) quartile and the third (75%) quartile, respectively. Small circles beyond the horizontal bars illustrate the outlier data, which begins at the value of the interquartile range multiplied by 1.5 and extends beyond.

The area under ROC curve (AUC) characterizing discrimination of osteoporosis was calculated separately for each clinical site and for each feature of the set P1–P10 as displayed in Fig. 3. This plot demonstrates the variability of diagnostic effectiveness of the analyzed parameters from site to site. The BMI, mean subject age, ethnicity and health conditions of enrolled subjects can contribute in that variability (see Table 1). Nine trained operators, from 2 to 5 members of the staff at each site were collecting the data with the BUSS. The value below 50% means that some parameters gave negative contributions for the specific site, for example, site 2 has negative contributions from parameters P7 and P9. Another observation is that combined AUC value is not the average value for all three sites even taking into account the weight coefficients for the number of subjects at the site. One may observe in Fig. 3 relatively wide deviation in diagnostic significance of parameter P7 and P10 (BMI) from site to site. Four of 10 parameters reach the 70% mark in Fig. 3. The variability of diagnostic accuracy between clinical sites might be explained by differences in clinical characteristics of subjects enrolled at the sites, however group specific deviations in bone quality cannot be excluded.

Fig. 4 presents the calculated sensitivity, specificity, and AUC for the output of the linear classifier (*BQI*) at each clinical site. Seven parameters have been used as input parameters for the linear classifier (eq. 3) as described in the Materials and Methods section. We found the sensitivity to range from 83.1% to 87.8%, specificity from 57.4% to 64.5%, and AUC from 70.9% to 83.0%. Parameters P2, P5 and P7 were excluded from *BQI* calculation. Site 1 shows relatively lower performance; though the data convergence from site to site is observed in Fig. 3.

The boxplot and ROC curve for output of linear BUSS classifier employed for differentiation of osteoporotic vs osteopenic/normal cases for clinical data was combined from all the sites and is illustrated in Fig. 5. Again, parameters P2, P5 and P7 were excluded from *BQI* calculation. The AUC is equal to 83.0% with p-value of 0.0000001. We observed no confidence interval overlapping for the mean values of the boxplots. Even interquartile ranges had no intersections. Four outliers are present in the normal group.

Fig. 3 demonstrates the limited discrimination capability of the selected parameters when analyzed individually due to the possible influence of numerous factors, such as, tibia vs spine bone quality, DXA limited accuracy, subject bone specific anatomy and deviation in the examination technique. The combined outcome for the seven parameters demonstrates an improvement in BUSS diagnostic capability. Further enhancement of BUSS diagnostic potential might be achieved by conducting larger scale clinical studies to get more data needed for “tuning” BUSS parameters and optimizing BUSS classifier. However, the main factor limiting progress in optimization of BUSS technology is that DXA T-score, an acknowledged indicator of the generalized form of osteoporosis is far from perfect, especially for the goals of the current study. The problem is that there are significant differences in the physical basis of DXA sensitivity in defining osteoporosis and that of BUSS. The BMD measured by DXA is a complex indicator of the bone mineral content in the planar projection of the bone or a sum of total contributions of the tissue mineralization,

thickness of bone and internal porosity. The BMD of DXA is not specific to individual changes of the bone thickness and porosity that may lead to erroneous conclusions in the cases of thick but porous bones such as observed in patients with diabetes [4]. On the contrary, the low and high frequency BUSS parameters can provide differential sensitivity to changes of the cortical thickness and the intracortical porosity. Future studies aimed at measuring the correlation between BUSS parameters and individual factors of bone atrophy – thinning of the cortex and increase of the intracortical porosity evaluated by quantitative computed tomography, should be considered.

Another source of discrepancy between characterization of bone by BUSS and DXA is use of different anatomic sites and the types of examined bone. Though the proximal tibia involves some areas of the prevalent spongy bone in the most upper region, the main type of the bone assessed by BUSS is the compact bone, where atrophic processes may be delayed and have different manifestations than those in the spongy bone of vertebrae assessed by DXA.

The data obtained in the current study does not allow making direct comparison of diagnostic potential of BUSS with that of DXA. However one may make an indirect comparison of BUSS and heel QUS, which is considered to be comparable to DXA in predicting fracture risk [7, 8]. The published data on heel QUS sensitivity and specificity to osteoporosis with reference to spine and/or hip T-scores of DXA [8] are 79% and 58% respectively, while these values for BUSS are 87% and 63% for a cohort of 331 subjects (see Fig. 4).

Conclusion

This study confirms the potential of BUSS to become an efficient adjunct to conventional tools for osteoporosis detection and a cost-effective technique in the diagnostics of bone health. The fact that DXA and multi-frequency scanning BUSS are sensitive to different bone characteristics involved in development of osteoporosis would suggest that the combined approach may have a much greater potential in predicting osteoporosis-related fractures. Larger population-based clinical validation of BUSS would be needed to confirm findings of this study and further broaden applicability of the new technique.

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Used Abbreviations

AUC	Area under ROC curve
BMD	Bone Mineral Density
BMI	Body Mass Index
BQI	Bone Quality Index
BUSS	Bone UltraSonic Scanner

DXA	Dual-energy X-ray Absorptiometry
ROC	Receiver Operating Characteristic

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Highlights

- Multi-frequency axial scanning ultrasonometer acquires wave propagation profiles along the proximal tibia
- Diagnostic parameters derived from the profiles at different frequencies were compared with DXA data in postmenopausal women
- Integral linear classifier provided 87.7% sensitivity and 63.2% specificity to DXA-identified osteoporosis

Fig. 1.
BUSS examination. See text.

Fig. 2. Boxplots for osteoporosis group (DXA spine T-score -2.5) and osteopenic/normal group (DXA spine T-score >-2.5) for BUS parameters P1–P10 (see text).

Fig. 3. ROC curve area of BUSS osteoporosis detection individually for the 3 clinical sites and combined for 331 postmenopausal women in consideration of BUSS parameters P1 through P10.

Fig. 4. Sensitivity, specificity and area under ROC curve (AUC) of BUSS osteoporosis detection individually for the 3 clinical sites and combined for 331 postmenopausal women with the use of liner classifier. Seven of ten parameters were used in calculation (see text).

Fig. 5. Boxplot and ROC curve of osteoporosis discrimination for the linear classifier output (*BQI*). Seven of ten BUSS parameters were used as input data for the classifier. Osteoporosis Detection in Postmenopausal Women using Axial Scanning Multi-Frequency Bone Ultrasonometer: clinical findings

Table 1

Subject enrollment, exclusion and clinical characteristics

Relevant data	Clinical Site			Total
	Site 1	Site 2	Site 3	All sites
Enrolled postmenopausal women, N (%)	66	150	122	338 (100%)
Excluded subjects due to BMI>35.0 kg/m ² , N (%)	2	3	2	7 (2.1%)
Final number of subjects in data analysis, N (%)	64	147	120	331 (97.9%)
Women with DXA spine T-score ≤ -2.5 (osteoporosis), N (%)	29	15	21	65 (19.6%)
Women with DXA spine T-score > -1.0 (normal), N (%)	22	76	57	155 (46.8%)
Mean age $\pm$ SD (years)	65.6 $\pm$ 12.6	69.8 $\pm$ 9.7	65.9 $\pm$ 9.3	67.6 $\pm$ 10.4
BMI $\pm$ SD (kg/m ²)	27.7 $\pm$ 4.3	27.0 $\pm$ 4.2	25.1 $\pm$ 4.6	26.6 $\pm$ 4.4
Race/ethnicity (% white)	100	100	74	90

Table 2

Analyzed BUSS parameters for osteoporosis detection

Parameter number	Parameter explanation	Units of measurements	Tibia zone for parameter calculation	Tibia bone structure at the analyzed zone
P1	Signal amplitude 60 kHz	Relative units	Proximal (zone 1)	Trabecular (spongy)
P2	Signal amplitude 100 kHz	Relative units	Distal (zone 3)	Compact
P3	Signal position 400 kHz	Relative time units	Proximal (zone 1)	Trabecular (spongy)
P4	Wave affinity index 60 kHz	Dimensionless	Zones 1–3	Combination
P5	Wave affinity index 400 kHz	Dimensionless	Zones 1–3	Combination
P6	Signal amplitude 1200 kHz	Relative units	Distal (zone 3)	Compact
P7	Signal amplitude ratio 800/60 kHz	Dimensionless	Zone 2	Transition
P8	Signal amplitude ratio 60/100 kHz	Dimensionless	Zone 2	Transition
P9	Signal center frequency shift 100 kHz	kHz	Distal (zone 3)	Compact
P10	Body Mass Index	kg/m ²	Not applicable	Not applicable

Table 3
Assessment of diagnostic significance in osteoporosis detection vs DXA spine T-score for BUSS parameters P1–P10

<i>Specific measure</i>	<i>Parameter</i>									
	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10
Area under ROC curve, %	70.2	65.6	68.2	68.3	60.2	58.1	60.2	59.6	63.9	62.4
Correlation with DXA spine T-score, R	0.22	0.20	0.20	0.34	0.22	0.13	0.05	0.04	0.16	0.30
<i>t</i> -test significance, p	1*10 ⁻⁴	3*10 ⁻⁴	4*10 ⁻⁴	1*10 ⁻⁶	0.009	0.011	0.096	0.040	0.001	6*10 ⁻⁴
<i>t</i> -test, h ($\alpha=0.05$)	1	1	1	1	1	1	0	1	1	1

Table 4

Mutual correlation coefficients (R) for BUSS parameters P1–P10

Parameter		Parameter								
Parameter	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10
P1	1	0.51	0.35	0.34	0.20	0.13	0.03	0.23	0.02	0.04
P2	0.51	1	0.29	0.27	0.17	0.20	-0.20	-0.25	0.01	0.02
P3	0.35	0.29	1	0.38	0.39	-0.08	0.08	-0.10	0.13	0.04
P4	0.34	0.27	0.38	1	0.62	-0.17	-0.07	-0.09	-0.05	0.03
P5	0.20	0.17	0.39	0.62	1	-0.22	-0.05	-0.16	0.03	0.29
P6	0.13	0.20	-0.08	-0.17	-0.22	1	0.12	-0.03	-0.06	-0.20
P7	0.03	-0.20	0.08	-0.07	-0.05	0.12	1	0.17	-0.01	-0.08
P8	0.23	-0.25	-0.10	-0.09	-0.16	-0.03	0.17	1	-0.11	-0.06
P9	0.02	0.01	0.13	-0.05	0.03	-0.06	-0.01	-0.11	1	-0.04
P10	0.04	0.02	0.04	0.03	0.29	-0.20	-0.08	-0.06	-0.04	1