Published in final edited form as:

Ultrasonics. 2009 March ; 49(3): 331–337. doi:10.1016/j.ultras.2008.10.003.

Application of the Dual-Frequency Ultrasonometer for Osteoporosis Detection

Armen Sarvazyan^a, Alexey Tatarinov^a, Vladimir Egorov^a, Souren Airapetian^a, Victor Kurtenok^a, and Charles J. Gatt Jr^b

^a Artann Laboratories, New Jersey, USA

^b Orthopaedic Research Laboratories, UMDNJ-Robert Wood Johnson Medical School, New Jersey, USA

Abstract

The paper presents results of a clinical validation study of Bone UltraSonic Scanner (BUSS), a novel dual-frequency axial transmission ultrasonometer, developed by Artann Laboratories. Assessment of bone conditions is based on evaluating relative changes of the axial profiles of ultrasonic characteristics in long bones and utilizes bulk and guided acoustic waves. The objective of this study was to determine the ability of BUSS to discriminate osteoporosis development stages. A total of 93 menopausal and post-menopausal women divided into five groups from normal to advanced osteoporosis according to their DXA hip t-score were enrolled in the study. The 2D waveform profiles at low (0.1 MHz) and high (1 MHz) frequencies were obtained by scanning 15 cm along the proximal tibia.

A multi-parametric linear classifier based on a set of the parameters derived from 2D acoustic waveform profiles has been developed. The efficiency of this classifier in differentiating osteoporosis from a normal sample was assessed using a Receiver Operating Characteristic (ROC) curve analysis. Based on the ROC analysis, BUSS demonstrated 76% sensitivity and 70% specificity to DXA-identified osteoporosis. The area under the ROC curve, which is a measure of how well a parameter can distinguish between the two diagnostic groups (diseased/normal) was 79.3%. The study confirmed BUSS's capability to discriminate between stages of bone atrophy and in particular to distinguish early changes induced by osteoporosis.

Keywords

Bone quantitative ultrasound; axial scanning; guided waves; osteoporosis

Introduction

Osteoporosis, induced by aging, as well as a side effect of certain drugs, is a serious public health problem. Osteoporosis is characterized by the microarchitectural disruption of bone and skeletal fragility, resulting in an increased risk of fracture [1]. Early diagnosis and controlled treatment could largely prevent complications associated with osteoporosis, such as

Corresponding author: Armen Sarvazyan, Ph.D., Dc.S., Artann Laboratories, 1459 Lower Ferry Rd, Trenton, NJ 08618-1414, Tel.: 609-333-0710; fax: 609-333-0712. armen@artannlabs.com.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

debilitating hip fractures. Despite this recognized need, the lack of affordable diagnostic technology leaves 90% of at risk patients undiagnosed and untreated [2]. Development of a portable, inexpensive, safe and user friendly diagnostic technique can aid in the screening and monitoring of bone condition in osteoporosis, as well as in the wider scope of metabolic diseases such as renal, endocrine, and gastrointestinal while providing control over the temporal effects of medications on the bone. Bone quantitative ultrasound (QUS), a simple, safe, and cost-effective technique sensitive to both mechanical and structural features of the bone has the potential of becoming an efficient tool to improving the assessment of bone fracture risk [3–5].

The heel QUS devices assess trabecular structure in the calcaneus bone by measuring the bulk (called also compressional or longitudinal) wave velocity and broadband attenuation slope (BUA) in the through transmission mode [6]. Clinical studies demonstrated strong correlation between BUA and fracture incidence in elderly population [7]. Axial QUS devices exploit acoustic waves propagating in the cortical layer of long bones, such as tibia, radius and phalanges, along the bone axis [8,9]. Commercial QUS devices of this type are mainly based on measurements of velocity of longitudinal ultrasonic wave in the megahertz frequency range. Velocity of this fastest type of wave varies in 3500–4200 m/s range in the compact bone. Although it was found that the longitudinal wave velocity in axial transmission has some correlation with both cortical thickness and bone mineral density [10], in general, the existing axial QUS devices employing only longitudinal waves, are not very effective in osteoporosis assessment [11–13].

Recently, multiple attempts to assess cortical thickness as an important factor of bone strength in addition to its elasticity by means of guided waves at low frequencies (0.1–0.3 MHz) have been undertaken [14–17]. These slow type waves have similarity to the flexural or zero-antisymmetric Lamb waves in plates, velocity of which strongly depends on the plate thickness in the case when the ultrasonic wavelength is greater than the latter [18]. In long bones, where the cortex is composed of the compact bone, the guided wave phase velocity correlates with the cortical thickness [19]. In a study involving healthy and osteoporotic subjects, the velocity of guided wave differed significantly between the two groups, whereas the first arriving longitudinal wave velocity did not, suggesting the former to be a more sensitive indicator of osteoporosis [14]. Increased interest to guided waves in the cortical bone in the last few years resulted in a surge of publications addressing theoretical and experimental aspects of the problem [20–23]. However, these interesting developments which might lead to a separate assessment of factors related to bone strength, such as cortical thickness and material properties, are not yet implemented in the commercial devices (IGEA DBM Sonic and Beamed Omnisense) [24].

The QUS technology described in this paper includes a combination of several new features [25]: the simultaneous use of various modes of acoustic waves generated in frequency band from 0.1 to 1 MHz; axial scanning mode of bone examination; and comprehensive analysis of waveforms of ultrasound signals propagating axially in the bone. An ultrasonic pulse transmitted along the bone travels in the form of bulk, surface, and various types of guided acoustic waves. These modes of acoustic waves are differentially sensitive to the mechanical (hardness), microstructural (porosity), and geometrical or macro-structural (cortical thickness) properties of bone.

To separate the contribution of the different modes of acoustic wave in the received signals and to evaluate their propagation parameters, it is necessary to make measurements at different frequencies. Changing the frequency of the acoustic pulse changes the ratio of the acoustic wavelength and the cortical thickness. This change results in the redistribution of contributions of different modes of acoustic waves in the received signal. Thus, at the frequency of 0.1 MHz,

the received ultrasonic waveform is defined mainly by the propagation parameters of the guided wave. The velocity of guided waves strongly depends on the cortical thickness. As a result, axial profiles of the guided wave velocity show a steep slope of the velocity-thickness dependence in the proximal part of the tibia, where the cortex is thinner than in the diaphysis. In contrast, the received waveform of an ultrasound pulse with 1 MHz carrier frequency is defined mainly by the propagation parameters of longitudinal wave. Velocity of the longitudinal wave is determined by the material properties, that by the bone Young's modulus [17,26,27]. Axial scanning, a new feature implemented in BUSS, allows assessment of topography of acoustical properties of long bones.

Detailed analysis of existing commercial ultrasonic devices can be found in [3,5,6,8,24] and the most widely used bone ultrasonometers are heel QUS devices. In contrast to the heel QUS that characterizes properties of the trabecular network of spongy bone in the calcaneus, BUSS focuses on the cortical bone of long bones. The anatomical region-of-interest of the current BUSS system is the proximal tibia, where the cortical thickness has a steep axial gradient. It is an allied site to the proximal femur, where osteoporotic fractures of the femoral neck are the most dramatic manifestation of the disease. In generalized osteoporosis, the similar changes revealing in the thinning of the cortex and in increase of the cortical porosity may occur in both sites in parallel. As compared to axial QUS devices, such as Sunlight Omnisense [8,10,24], measuring the only longitudinal wave velocity in long bones, BUSS provides with a wider scope of diagnostic information important for fractures risk prediction owing to dual-frequency examination, processing of larger portions of received ultrasonic waveforms and assessment of topography by the axial scanning.

Our previous studies on phantoms, modeling gradually progressing porosity from the inner area of the cortical layer, confirmed the possibility of the detection of these changes in the inner layer of the phantom by means of the guided waves at low frequency on the order of 100 kHz [17]. At a higher frequency (500 kHz), the response was affected by the porosity changes only when these changes reached the outer layer. Thus, the combined use of low and high frequency data may provide a possibility of discriminating the character and stages of the bone deterioration process. The purpose of the present work was to confirm the laboratory findings on phantom studies in the human study and investigate the ability of BUSS to assess osteoporosis in a pilot clinical study involving a limited number of patients.

Materials and Methods

Subjects

The pilot clinical study has been conducted at the Robert Wood Johnson Medical Center, University of Medicine and Dentistry of New Jersey, under the IRB approval # 4826. The patient population consisted of women of menopausal, post-menopausal, and senile ages. 129 patients ranging by age from 53 to 74 years were examined. The patients with the Body Mass Index (BMI) greater than or equal to 30 kg/m² (36 patients) were excluded from the cohort due to the data obtained from these patients being substantially different from the common cohort. In these cases, the thicker layer of soft tissues layer covering the tibia caused prevalent propagation of the ultrasound in the soft tissues. As a result, the diagnostically relevant characteristic features of the signal corresponding to the guided ultrasonic waves in long bones were significantly distorted or masked. Hence, the data on the remaining 93 patients with BMI ranging from 18.8 to 29.9 kg/m² were only used in the data analysis. The patients were classified into groups of 'norm', 'osteopenia', and 'osteoporosis', with sub-groups of 'norm' and 'osteopenia' according to the DXA t-score of the hip (Table 1). Additional sub-division of groups "norm" and "osteopenia" was based on the differences in the DXA t-score was made in order to have more gradations of bone condition for testing capability of BUSS to discern them, especially early changes.

The increase of average age from the groupings of norm to osteoporosis conformed to the common knowledge that the osteoporosis risk increases with aging. Meanwhile, the BMI distribution for all groups did not show significant differences.

Ultrasonic examination

Clinical studies were conducted using BUSS prototype shown in Fig. 1. The device consists of an ultrasonic probe, a data acquisition electronic unit connected to a laptop PC, a platform for supporting the tested extremity, and a probe motion tracker incorporated in the platform. The probe motion tracker is designed upon the principle of the measuring tape. An optical counter mounted in the motion tracker measures the extension of the stretched cord attached to the probe. Measurements in the axial transmission mode were realized by a transmitting and a receiving transducers placed unilaterally on the skin above the examined bone. In the present study, the dual-frequency regime was realized. Measurements were conducted at 0.1 MHz and 1.0 MHz, which will be further referred as low frequency (LF) and high frequency (HF), respectively. Records of the LF and HF ultrasonic signals synchronized to the traversed path along the bone were obtained during the stepwise manually-guided scanning of the bone.

The quality of examination highly depends on the quality of acoustical contact of the transducer with the skin above the tested bone. To provide necessary acoustical contact, the probe needs to be pressed into the skin with a sufficient force. Yet, at the same time, excessive pressing could cause pain and leave traces on the patient's skin. To assist the operator in providing adequate pressure, a real-time parameter based on the ultrasonic signal amplitude is displayed on the user interface. This parameter is proportional to applied contact pressure and ultrasonic signal accumulation begins after a predetermined threshold for 0.1 MHz signal amplitude has been reached. The value of the threshold was chosen as a trade-off between signal-to-noise ratio and applied force which as a rule does not exceed 0.5 kg. To facilitate measurements and minimize an operator's errors, an "examination quality index" has been introduced to evaluate the reliability of obtained results. The algorithm for evaluating the index is founded on the assumption that a profile graph of ultrasound velocity along the bone is a smooth function. Any sharp deviation of the calculated velocity for two neighboring points is considered an indication of measurement error due to deficient acoustic contact or inadequate manipulation of the probe. The standard deviation calculated from the plurality of deviations along the scanned trajectory is defined as an "examination quality index". When this index exceeds an empirically defined threshold of 15 m/s, the measurement is discarded and a feedback signal is displayed to the operator to repeat the scan.

The tibiae were scanned along the medial surfaces starting from the knee joint to 15 cm towards the diaphysis. This trajectory includes regions of bone with different proportions of compact and spongy types of bone structure, as well as a steep gradient of the cortical thickness. Changes of profiles of ultrasound propagation parameters provide information on changes of properties of each component of bone as well as on the spatial processes associated with bone deterioration.

Prior to the test, the axial trajectory was determined and marked on the skin. Ultrasonic measurements were taken with a step of 7 mm along the trajectory. This step of scanning was empirically determined as a trade-off between the requirement of having sufficient data points for obtaining smooth axial profiles of acoustic parameters of the bone and not making the measurements procedure unnecessary long.

Silicon-based acoustic gel was used as a coupling medium.

Data processing

In conventional bone ultrasonometers, analysis of acquired ultrasonic signals is limited to obtaining ultrasound velocity and attenuation in the tested site of bone. Although these ultrasound propagation parameters are sensitive to changes in bone condition, they are insufficient for adequate characterization of a complex and highly variable object such as bone. Furthermore, the calculation of absolute values of acoustic parameters of bone using ultrasonic measurement data is based on numerous, often poorly defined, assumptions. An important innovation implemented in BUSS is that most of the parameters evaluated from ultrasonic data for bone assessment are only indirectly related to the absolute values of ultrasound propagation parameters. For example, instead of using sophisticated means for eliminating the error in evaluating speed of acoustic waves in bone due to the skin layer, as it is done in some conventional bone ultrasonometers [8], we selected several normalized parameters, described in the next section, which are minimally dependent on soft tissue contribution.

The BUSS software was designed to obtain diagnostic information by an analysis of the acquired ultrasonic waveform parameters as a function of position along the bone at each measurement frequency. The stages of BUSS data processing are shown in Fig. 2 and Fig. 3. The acquired signals at successive discrete points along the scanning trajectory are plotted as a 2D spatio-temporal map, in which the abscissa is the time of ultrasonic pulse propagation, the ordinate is the scanned distance along the bone, and the values are amplitudes of ultrasonic signal in arbitrary units. A 2D map is generated for both LF and HF ultrasonic pulses. Special algorithms have been developed for the sensitive detection of bone deterioration process, which modifies the spatial heterogeneity of the bone by affecting its structural components. An algorithm illustrated in Fig. 3 is based on finding the informative part of the received acoustic waveform to reveal the spatial features of bone deterioration process. The 2D spatio-temporal map of the acquired signal is filtered and analyzed to define the region of most significant shift of acoustic wave front called the Informative Signal Area (ISA). The ISA, is defined as a region of acquired signal 2-D map containing the steepest spatial gradients of the recorded acoustic wave fronts. After several further steps of image processing, including rectification, enveloping and setting the thresholds, the axial profile of acoustic wave fronts in the ISA is obtained. The processed 2D waveform profiles illustrated in panel (e) of Fig. 3 were used for evaluating the following quantitative parameters:

1. Proximity Indices at LF and HF ($PI-LF$ and $PI-HF$) showing the level of similarity of individual 2D waveform profiles to the averaged 2D waveform profiles for each bone condition defined below in Table 1, ranging from healthy bone to advanced osteoporosis. To calculate the proximity index, a pattern comparison method, the likelihood classifier, based on the method of normalized squared difference [28] was applied. Parameters $PI-LF$ and $PI-HF$ were evaluated using data processing algorithms provided by the Intel® Integrated Performance Primitives for Intel® Architecture (<http://developer.intel.com>) in part “Proximity Measures of an Image and a Template” were used, being integrated into BUSS software. The template for norm and osteoporosis were obtained as statistical average 2D waveform profiles for the groups Norm 1 and Osteoporosis correspondingly, classified according to hip DXA t-score. The templates can be further adjusted with more clinical data accumulated. The proximity indices were dimensionless coefficients ranging from 5 to 150 at LF and from 5 to 250 at HF, the smallest values of which showed similarity to the normal condition (Norm1 group average) and the highest values corresponded to proximity to osteoporosis (Osteoporosis group average).¹¹
2. Normalized Intensities at LF ($I-LF$), and HF ($I-HF$) defined as average intensities of rectified, enveloped and normalized ultrasonic signals in ISA region. The values of $I-LF$ and $I-HF$ reflect the ratio of black and white areas in the 2D waveform profile

shown in Fig. 3(e). For calculating these parameters, signal amplitudes in each discrete point (pixel) within ISA were summed and the obtained sum of amplitudes was divided by number of pixels. In order to make measurements independent on the device settings, the signals were normalized by peak value in each line within ISA. Each signal is considered in the relative amplitude scale ranging from 0 to 128 according to maximally possible amplitude by 7-bit digitizing. The peak signal amplitude is reduced to 128, thus measurements are free of influence of variations of the absolute signal amplitude influenced by many factors, including contact pressure produced by an operator. The normalized signal intensities in ISA were used for quantification of BUSS's sensitivity in this pilot study. Parameter *I-LF* is determined mostly by propagation characteristics of the guided wave, while *I-HF* reflects properties of the longitudinal wave.

Statistical Analysis

A statistical assessment of BUSS diagnostic capability was completed with the aid of the statistical toolbox in MATLAB 6.1 (MathWorks, Natick, MA). For visual evaluation of the analyzed clinical data distributions within the normal and osteopenia/osteoporosis patient samples, we have used box plots for data representation. In descriptive statistics, the box plot is a convenient and widely accepted way of graphically depicting groups of numerical data or data samples [29]. Box plots are able to visually show distinctions of data samples without making any assumptions of the underlying statistical distribution. The spacings between the different parts of the box help to compare variance, median, quartiles, the data range. The box plot also identifies skewness (asymmetry) and outliers. We have used the notched box plot [29] showing a confidence interval for the median value. Intersection or divergence of confidence intervals for two patient samples is a visual analog of the paired t-test.

To evaluate diagnostic performance of the BUSS we used the receiver operating characteristic (ROC) curve analysis [30,31]. The area under the curve (AUC) is determined from plotting sensitivity vs. 1-specificity of a test as the threshold varies over its entire range. Conceptually, AUC is interpreted as the probability that the test will produce a value for a randomly chosen diseased subject that is greater than the value for a randomly chosen healthy subject [32]. Each data point on the ROC plot represents a particular setting of the threshold which is compared with classifier output. An area of 100% indicates a perfect prediction; an area of 50% is a chance result.

Results and Discussion

Fig. 4 shows the LF (100 kHz) waveform profiles obtained for patients' groups ranging from norm through stages of osteopenia to osteoporosis. Positions of the wave front marked by arrows in Fig. 4 denote changes of the guided wave arrivals due to gradual wave slowing with worsening of bone condition. The wave front position changes not only upon the time coordinate but also shifts along the tibia from the upper metaphysis towards the diaphysis. It is caused by thinning of the cortex by osteoporosis onset and decrease of the ratio of the cortical thickness to the ultrasonic wavelength. At early stages of osteoporosis, this decrease is more expressed in the bone areas closer to epiphysis, where the cortex is much thinner anatomically than in the diaphysis, and it's thinning to the same value causes higher relative changes to the ultrasonic wavelength. By further decrease of the cortical thickness, more areas of bone towards the diaphysis are involved. Thus, from the acoustical point of view, it is a classic manifestation of geometrical dispersion of guided or flexural (A0 Lamb) wave velocity in a thin walled shell [20,21]. Another feature presented by the sequence of 2D waveform profiles in Fig. 4 is that the differences between gradations of upper and lower norm and between norm and early

osteopenia are more pronounced than the differences between gradations of mild and severe osteopenia, as well as the difference between osteopenia and osteoporosis.

At HF of 1 MHz, the ratio of the cortical thickness to ultrasonic wavelength is much higher than at 100 kHz, and the HF waveform profiles are less dependent on changes of the cortical thickness. The HF waveform profiles are formed by the fast propagating longitudinal wave, and the propagation parameters of these waves vary much less along the bone than that of the LF guided wave. This result can be explained by the fact that the material properties of bone substance are varied by osteoporosis not as significantly as the attenuation of HF waves which can be highly affected by the increased inner porosity of bone.

The quantitative parameters derived from LF and HF signals can provide differentiation of bone conditions, as it seen for the data presented in Table 2. The values of these parameters continuously change in patients' groups from norm to osteoporosis. Meanwhile, character of changes of LF and HF parameters differs. *I-LF* decreases steadily even at early stages of "worsening" of bone condition, while sharp decrease of *I-HF* is noted only in the advanced osteopenia and osteoporosis. This finding agrees with the notion that the parameter *I-LF* related to propagation of guided waves is sensitive to bone thinning sensed by guided waves, while changes in *I-HF* reflect degradation of the compact bone by increased inner porosity. Cross correlation between *I-LF* and *I-HF* involving all patients data is rather poor (Pearson linear correlation coefficients $r=0.48$) that allows considering LF and HF parameters independent.

A multi-parametric linear classifier based on a set of the parameters shown in Table 2, has been developed. The patients were subdivided into two groups of normal sample cases (41) and osteopenia/osteoporosis cases (52) according to the hip DEXA t-score. The box plot in Fig. 5A exhibits a statistical summary of the classifier output for discrimination of normal and diseased cases. The statistical summary of variables includes the median, quartiles, range, and outlying extreme values. The confidence intervals between the selected groups did not overlap. The efficiency of this classifier in differentiating osteoporosis from a normal sample was assessed using a Receiver Operating Characteristic (ROC) [30] curve analysis as shown in Fig. 5B. The confidence interval for the ROC curve was evaluated by a modified "fixed-width" bands method [28]. Based on the ROC analysis, BUSS demonstrated 76% sensitivity and 70% specificity to DXA-identified osteoporosis. The area under the ROC curve is 79.3%. This area is a measure of how well a parameter can distinguish between the two diagnostic groups (diseased/normal) while a ROC curve area of 100% corresponds to absolute separation.

In general, there is poor agreement between data provided by existing commercial QUS of the axial type in long bones and bone status assessed by DXA, as revealed by Kappa and ROC analyses [12,33]. Consequently, the conventional QUS, especially axial QUS, is hardly ever used for monitoring the bone condition in metabolic diseases or for predicting fracture risk. However, the current study suggests that the reason for low efficiency of conventional ultrasonic devices in bone assessment could be that they use only a small fraction of diagnostically relevant information hidden in acoustic signals propagating through the bone. Results of this study indicate that through a multi-parametric acoustic evaluation of bone with the simultaneous use of various modes of ultrasonic waves the diagnostic capabilities of QUS may increase in comparison to the conventional methods that employ only bulk waves operating at a single carrier frequency of the probing ultrasonic pulse. Our previous studies on phantoms and animal bones demonstrated that comprehensive analysis of changes in broadband acoustic waveforms propagating in the bone may provide information on cortical thickness, intra- and sub-cortical porosity, as well as on the bone matrix mineralization [17]. Based on the results of these laboratory studies an optimistic projection has been made on BUSS potential to effective assess bone conditions. Results of presented clinical study confirmed these projections.

Conclusions

The study confirmed BUSS's capability to discriminate between stages of bone atrophy and, in particular, to distinguish early changes induced by developing osteoporosis. This early stage of bone deterioration is not as clearly distinguished by any other currently available QUS technique. 2D spatio-temporal waveform profiles provided by BUSS are shown to be an effective indicator of the atrophic processes.

Acknowledgments

Research supported by the National Institute of Health under Grant No. G017400 and NASA contract No. NAS3-02167. The authors are grateful to Dr. N Sarvazyan for useful discussions.

References

1. Lin JT, Lane JM. Osteoporosis: a review. Clin Orthop Relat Res 2004;425:126–34. [PubMed: 15292797]
2. Nguyen TV, Center JR, Eisman JA. Osteoporosis: underrated, underdiagnosed and undertreated. Med J Aust 2004;180(5 Suppl):S18–S22. [PubMed: 14984358]
3. Glüer CC, Barkmann R. Quantitative ultrasound: use in the detection of fractures and in the assessment of bone composition. Curr Osteoporos Rep 2003;1(3):98–104. [PubMed: 16036071]
4. Njeh CF, Fuerst T, Diessel E, Genant HK. Is quantitative ultrasound dependent on bone structure? A reflection. Osteoporos Int 2001;12(1):1–15. [PubMed: 11305077]
5. Laugier P. Instrumentation for in vivo ultrasonic characterization of bone strength. IEEE Trans Ultrason Ferroelectr Freq Control 2008;55(6):1179–96. [PubMed: 18599407]
6. Gregg EW, Kriska AM, Salamone LM. The epidemiology of quantitative ultrasound: a review of the relationships with bone mass, osteoporosis and fracture risk. Osteopor Int 1997;7:89–99.
7. Bauer DC, Gluer CC, Cauley JA, Vogt TM, Ensrud KE, Genant HK, Black DM. Broadband ultrasound attenuation predicts fractures strongly and independently of densitometry in older women. A prospective study. Study of Osteoporotic Fractures Research Group. Arch Intern Med 1997;157(6):629–34. [PubMed: 9080917]
8. Hans, D.; Bo, F.; Fuerst, T. Non-heel quantitative ultrasound devices. In: Njeh, CF.; Hans, D.; Fuerst, T.; Gluer, CC.; Genant, HK., editors. Quantitative Ultrasound: Assessment of Osteoporosis and Bone Status. Martin Dunitz; London: 1999. p. 145-162.
9. Camu E, Talmant M, Berger G, Laugier P. Analysis of the axial transmission technique for the assessment of skeletal status. J Acoust Soc Am 2000;108:3058–3065. [PubMed: 11144598]
10. Prevrhal S, Fuerst T, Fan B, Njeh C, Hans D, Uffmann M, Srivastav S, Genant HK. Quantitative ultrasound of the tibia depends on both cortical density and thickness. Osteoporos Int 2001;12(1):28–34. [PubMed: 11305080]
11. Hollevoet N, Verdonk R, Goemaere S, Van Maele G. Tibial ultrasound velocity in women with wrist fracture. J Clin Densitom 2004;7(3):302–6. [PubMed: 15319501]
12. Christian R, Krestan CR, Grampp S, Henk C, Peloschek P, Imhof H. Limited diagnostic agreement of quantitative sonography of the radius and phalanges with dual-energy x-ray absorptiometry of the spine, femur, and radius for diagnosis of osteoporosis. AJR 2004;183:639–644. [PubMed: 15333350]
13. Tuna H, Birtane M, Ekuklu G, Cermik F, Tuna F, Kokino S. Does quantitative tibial ultrasound predict low bone mineral density defined by dual energy X-ray absorptiometry? Yonsei Med J 2008;49:436–42. [PubMed: 18581594]
14. Nicholson PH, Moilanen P, Karkkainen T, Timonen J, Cheng S. Guided ultrasonic waves in long bones: modelling, experiment and in vivo application. Physiol Meas 2002;23(4):755–76. [PubMed: 12450274]
15. Lefebvre F, Deblock Y, Campistron P, Ahite D, Fabre JJ. Development of a new ultrasonic technique for bone and biomaterials in vitro characterization. J Biomed Mater Res 2002;63:441–6. [PubMed: 12115753]

16. Muller M, Moilanen P, Bossy E, Nicholson P, Kilappa V, Timonen J, Talmant M, Cheng S, Laugier P. Comparison of three ultrasonic axial transmission methods for bone assessment. *Ultrasound Med Biol* 2005;31(5):633–642. [PubMed: 15866413]
17. Tatarinov A, Sarvazyan N, Sarvazyan A. Use of multiple acoustic wave modes for assessment of long bones: model study. *Ultrasonics* 2005;43(8):672–80. [PubMed: 15982472]
18. Viktorov, IA. *Physical Theory and Applications*. Plenum Press; New York: 1967. Rayleigh and Lamb Waves; p. 67-117.
19. Moilanen P, Nicholson PH, Kilappa V, Cheng S, Timonen J. Assessment of the cortical bone thickness using ultrasonic guided waves: modelling and in vitro study. *Ultrasound Med Biol* 2007;33(2):254–62. [PubMed: 17306696]
20. Moilanen P. Ultrasonic guided waves in bone. *IEEE Trans Ultrason Ferroelectr Freq Control* 2008;55:1277–86. [PubMed: 18599415]
21. Bossy E, Talmant M, Laugier P. Three-dimensional simulations of ultrasonic axial transmission velocity measurement on cortical bone models. *J Acoust Soc Am* 2004;115:2314–24. [PubMed: 15139643]
22. Protopappas VC, Fotiadis DI, Malizos KN. Guided ultrasound wave propagation in intact and healing long bones. *Ultrasound Med Biol* 2006;32:693–708. [PubMed: 16677929]
23. Sasso M, Haïat G, Talmant M, Laugier P, Naili S. Singular value decomposition-based wave extraction in axial transmission: application to cortical bone ultrasonic characterization. *IEEE Trans Ultrason Ferroelectr Freq Control* 2008;55(6):1328–32. [PubMed: 18599420]
24. Krieg MA, Barkmann R, Gonnelli S, Stewart A, Bauer DC, Del Rio Barquero L, Kaufman JJ, Lorenc R, Miller PD, Olszynski WP, Poiana C, Schott AM, Lewiecki EM, Hans D. Quantitative ultrasound in the management of osteoporosis: the 2007 ISCD Official Positions. *J Clin Densitom* 2008;11:163–87. [PubMed: 18442758]
25. Sarvazyan, A.; Tatarinov, A. Method and device for multiparametric ultrasonic assessment of bone conditions. US patent. 6,468,215 B1. 2001.
26. Tatarinov A, Sarvazyan A. Topography of acoustical properties of long bones: from biomechanical studies to bone health assessment. *IEEE Trans Ultrason Ferroelectr Freq Control* 2008;55(6):1287–97. [PubMed: 18599416]
27. Tatarinov, A.; Sarvazyan, A. Dual-frequency method for ultrasonic assessment of bones: model study. *Proceedings of the World Congress on Ultrasonics*; September 2003; 2003. p. 895-898.CDROM
28. Patrick, EA. *Fundamentals of Pattern Recognition*. Prentice-Hall; Englewood Cliffs, New Jersey: 1972.
29. McGill R, Tukey JW, Larsen WA. Variations of Box Plots. *American Statistician* 1978;32:12–16.
30. Zweig MH, Campbell G. Receiver-operating characteristic (ROC) plots: a fundamental evaluation tool in clinical medicine. *Clin Chem* 1993;39:561–577. [PubMed: 8472349]
31. Streiner DL, Cairney J. What's under the ROC? An introduction to receiver operating characteristics curves. *Can J Psychiatry* 2007;52(2):121–28. [PubMed: 17375868]
32. Macskassy, SA.; Rosset, F. ROC Confidence Bands: An Empirical Evaluation. *Proc. 22nd Intern. Conf. Machine Learning*; Bonn, Germany. 2005. p. 537-54.
33. Cook RB, Collins D, Tucker J, Zioupos P. The ability of peripheral quantitative ultrasound to identify patients with low bone mineral density in the hip or spine. *Ultrasound Med Biol* 2005;31(5):625–32. [PubMed: 15866412]

Fig. 1.
Bone UltraSonic Scanner (BUSS): A – general view; B – ultrasonic probe; C – application layout: 1- ultrasonic probe; 2- probe motion tracker; 3- stretched cord of the motion tracker; 4- support platform; 5- scanning trajectory.

Fig. 2.
Acquisition of 2D ultrasonic signal sets by stepped scanning of proximal tibia.

Fig. 3. Stages of ultrasonic signals processing for obtaining 2D spatio-temporal waveform profiles in Informative Signal Area (ISA).

Fig. 4.
Averaged osteoporosis related alterations of 2D waveform spatio-temporal profiles for guided waves at LF (100 kHz) in proximal tibiae.

Fig. 5. Statistical data analysis: A – A box plot representing the group of normal patients (41 cases) and the group of osteopenia/osteoporosis patients (52 cases); B - ROC curve for BUSS osteoporosis detection by the multi-parametric classifier in comparison to DXA detected osteoporosis. The area under the ROC curve is 79.3%.

Table 1

Patients' grouping according to hip DEXA t-score

Group	N	Hip DEXA t-score	Age, years	BMI, kg/m ²
Norm 1	15	> -0.3	55 ± 9	23.6 ± 3.4
Norm 2	26	-0.3 ÷ -0.9	59 ± 9	24.6 ± 2.7
Osteopenia 1	23	-1.0 ÷ -1.7	63 ± 12	23.5 ± 5.6
Osteopenia 2	16	-1.8 ÷ -2.5	65 ± 10	24.1 ± 2.9
Osteoporosis	13	< -2.5	66 ± 10	23.7 ± 2.6

Table 2

BUSS parameters (in relative units) in patients' groups

Group	I-LF	I-HF	PI-LF	PI-HF
Norm 1	20.4 ± 10.1	17.4 ± 8.1	21 ± 14	87 ± 27
Norm 2	17.9 ± 6.6	19.3 ± 8.5	23 ± 12	104 ± 43
Osteopenia 1	14.0 ± 8.2	13.5 ± 6.9	57 ± 44	133 ± 58
Osteopenia 2	11.9 ± 5.3	12.4 ± 6.7	73 ± 48	141 ± 52
Osteoporosis	10.6 ± 3.0	13.6 ± 7.0	76 ± 42	159 ± 47