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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.

1. 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 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

Abbreviations: AUC, area under ROC curve; BMD, bone mineral density; BMI, body mass index; BQI, Bone Quality Index; BUSS, bone ultrasonic scaner; DXA, dual-energy X-ray absorptiometry; ROC, receiver operating characteristic.

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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.

2. Materials and methods

2.1. 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/m^2; 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.

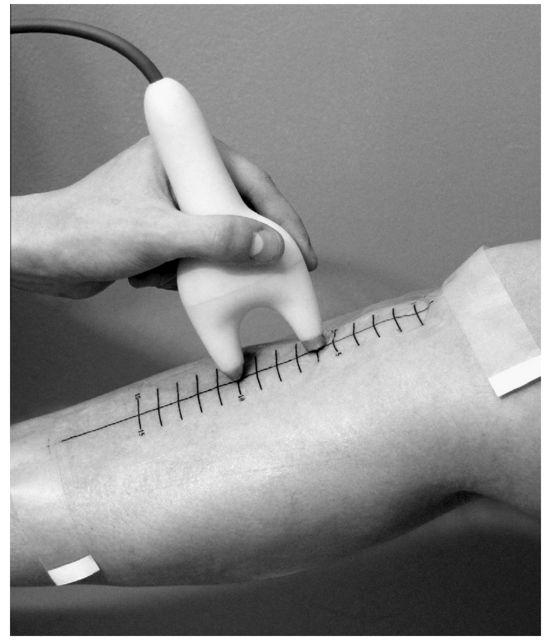

Fig. 1. BUSS examination. See text.

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.

2.2. 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

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