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Ultrasonic Diagnosis of Osteoporosis

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Abstract

Osteoporosis is a skeletal disease characterized by two factors: reduced bone mass and microstructure disruption of bone tissue. These symptoms increase bone fragility and can contribute to eventual fracture. In recent years, quantitative ultrasound (QUS) technologies have played a growing role in the diagnosis of osteoporosis. Most of the commercial bone sonometers measure speed of sound and/or broadband ultrasound attenuation at peripheral skeletal sites. However, QUS parameters are purely empirical measures that have not yet been firmly linked to physical parameters, such as bone strength or porosity, and the underlying physics for their variations in cancellous bone is not well understood yet. This paper reviews the QUS technologies for the diagnosis of osteoporosis and also addresses several theoretical models, such as the Biot model, the scattering model, the stratified model, and the modified Biot-Attenborough model, for ultrasonic wave propagation in bone.

Keywords: *Osteoporosis, Cancellous bone, Cortical bone, Bone mineral density, Ultrasound, Speed of sound, Broadband ultrasound Attenuation*

I. Osteoporosis

1.1. Definition of osteoporosis

Over the years, many definitions of osteoporosis have been suggested according to its nature and causes, as well as its specific skeletal abnormalities. In recent years, however, more consistent definitions have been developed, with definitions covering the spectrum of manifestations, from the reduced amount of bone present to some of the consequences of bone loss. A panel from the U.S. National Institute of Health Consensus Conference defined osteoporosis as 'a disease characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk' [1]. Osteoporosis is generally categorized as primary or secondary, depending on the absence or presence of associated medical diseases, surgical procedures, or medications known to be associated with accelerated bone loss.

Experts from the World Health Organization (WHO) proposed specific criteria for densitometric diagnosis of osteoporosis based on bone mineral content (BMC) and bone mineral density (BMD) at any skeletal site [1]. This criterion defines patients with osteoporosis as having a BMC or BMD value that is more than standard deviations (SDs) below the mean of normal peak bone mass. This makes possible a diagnosis of osteoporosis before the first fracture which appears as a complication of bone fragility. These are general guidelines for diagnosis but are not intended to require or restrict therapy for individual patients. Rather, the physician and the patient should use the BMD information in

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conjunction with knowledge of the patient's specific medical and personal history to determine the best course of action for each individual as a function of the lifetime fracture risk.

1.2. Diagnosis of osteoporosis

The susceptibility to fracture depends on a variety of factors, including bone mass, the propensity to fall, visual acuity, and response to falling. However, studies have shown that bone mass is the most important determinant of bone strength and accounts for up to 80 % of its variance [2]. Therefore, reduced bone mass is a useful predictor of increased fracture risk. Many prospective studies have shown that a decrease of 1 SD in bone density at the spine or hip increases the risk of fracture by a factor of two to three [3]. Therefore, methods of measuring BMD are pertinent to the detection of osteopenia, identification of those individuals at risk of atraumatic fracture, and assessment of the efficacy of either prevention or treatment of osteoporosis. Current techniques include: radiographic absorptiometry (RA), single energy x-ray absorptiometry (SEXA), dual energy x-ray absorptiometry (DEXA), quantitative computed tomography (QCT), and quantitative ultrasound (QUS) [4].

Today, the primary technique used in the diagnosis of osteoporosis is DEXA, which has been established as a reliable means of measuring BMD [5]. However, axial DEXA is generally restricted to the large medical practices with limited patient access. The problem also remains that BMD accounts for only about 75 % to 85 % of the variance in bone strength in normal bone [2]. Several bone properties such as microarchitecture or tissue elasticity which are not captured by conventional x-ray-based densitometry also contribute to bone strength independently of BMD [6]. The alternative to x-ray introduced in the 1980s for the clinical assessment of bone status is represented by QUS [7]. Recent significant growth in this industry was based on the potential of elastic waves to probe multiple bone properties including bone density, microarchitecture, and elasticity [8].

1.3. Cancellous and cortical bones

Anatomically, two forms of bone are distinguishable: the cortical (compact) and cancellous (trabecular or spongy) bones [1]. The cancellous bone consists of a three-dimensional lattice of branching bony spicules, or trabeculae, delimiting a labyrinthine system of interspaces that are occupied by bone marrow. The cortical bone appears as a solid continuous mass in which spaces can be seen only with the aid of a microscope. Two forms of bone grade into one another without a sharp boundary. Cortical bone has four times the mass of cancellous bone, although the metabolic turnover rate of cancellous bone is eight times higher than that of cortical because bone turnover is a surface event, and cancellous bone has a greater surface area than cortical bone. Although cancellous and cortical bones are constituted from the same cells and the same matrix elements, there are structural and functional differences between them. Cortical bone mainly fulfills the mechanical and protective functions, and cancellous bone the metabolic function. In general, cancellous bone is found in the axial skeleton (spine), small bones of the peripheral skeleton (calcaneus), and distal parts (epiphysis) of long bones such as radius and femur, while the diaphysis of long bones is composed primarily of cortical bone (radius, femur, tibia).

At the time of menopause, women begin to lose bone. Both types of bone tissue are sensitive to age-related bone resorption. Cortical bone usually becomes more porous with advancing age. In addition, the cortices of long bone become thinner. Cancellous bone loss leads to increased porosity, thinning of trabecular elements, and disruption of structure continuity. The age-related losses of both cancellous and cortical bones substantially increase the fragility of bone. Therefore, they are both appropriate to evaluate the risk of fracture. Like

x-ray-based densitometry, QUS technologies have been adapted to assess different skeletal sites [8]. The type of ultrasonic wave propagation and the nature of interaction between bone structure and ultrasound will be dependent on the skeletal site and the type of bone being investigated.

II. Quantitative Ultrasound Technology

The clinical potential of ultrasound for the investigation of pathological conditions that affect bone strength has been recognized as early as in the 1950s. In 1958, a method was described using the measurement of ultrasonic velocity of a wave propagating along the tibial crest for monitoring fracture healing, but no practical implementation occurred [9]. Modern bone QUS was initiated in 1984 by Langton *et al.* [7]. These authors reported that osteoporotic women could be discriminated from nonosteoporotic women by measuring the slope of the frequency-dependent attenuation between 200 and 600 kHz at the calcaneus. The measurement site at the calcaneus is composed mainly of highly porous cancellous bone. The calcaneus is the most popular measurement site and the majority of clinical reports have focused on this bone. Since that time, many advances have been observed in the measurement technique and devices are currently available to measure many skeletal sites (calcaneus, finger phalanges, tibia, radius, metacarpal) [8]. Because osteoporosis is a systemic disease, measurements of bone strength or of a surrogate marker (BMD or QUS parameters) at one anatomic site are generally predictive of fracture risk at other anatomic sites. For the time being, QUS technologies have focused measurements at easily accessible peripheral sites, *i.e.*, heel, finger, wrist, or tibia, where the impact of a thin layer of surrounding soft tissue is less of an issue.

In recent years, QUS technologies have played a growing role in the assessment of skeletal status. This development is attributable to the wide availability of ultrasonic equipment which provides equivalent fracture risk assessement compared to conventional x-ray absorptiometric techniques. Techniques based on ultrasound for bone assessment are less expensive, faster, simpler, and more portable than their x-ray counterparts. In addition, they produce no ionizing radiation. Most of the commercially available QUS devices measure speed of sound (SOS) and/or broadband ultrasound attenuation (BUA) at the calcaneus [8]. SOS is related in a predicted manner to elasticity and density of cancellous bone, whereas BUA is related to both density and structure. SOS and BUA are sometimes combined linearly into a single index such as stiffness or the quantitative ultrasound index [10]. This quantitative index has the advantage of combining information from ultrasonic attenuation and velocity, to be more stable in time and less sensitive to the influence of the temperature than either parameter SOS or BUA taken alone.

Commercial bone QUS devices have utilized transit time velocity measurements, with various definitions for the arrival time of the ultrasound signal at the receiving transducer [8]. There are different ways of defining the pulse arrival time with marked differences in the magnitude of the calculated velocity. These are the earliest detectable deviation from zero, the use of zero-crossing points, and the application of cross-correlation technique. It should be noted that all of the above transit time methods yield signal velocities, which are different from phase velocity, and that they may be influenced by the frequency of the transducers used [11]. In highly attenuating media like cancellous bone, frequency-dependent attenuation lowers the center frequency and broadens the pulse, and hence signal velocity depends on the marker used to define transit time. BUA is a measure of the frequency dependence of the attenuation and is defined as the slope of a linear fit to the measured frequency-dependent attenuation in units of dB/MHz [7]. Most published studies have used the frequency range of 0.2-1 MHz [1]. It is generally accepted that the frequency range

used has an upper limit set by attenuation and a lower limit set by the transducer bandwidth. It has now become the commercial norm to restrict measurements to the range of 0.2–0.6 MHz.

Through-transmission measurements of SOS and BUA only partially exploit the information related to the interaction between elastic wave and bone. The assessment of bone strength demands increasing specific knowledge about microscopic bone quality and structure [6]. From the theory and the previous experience of backscatter measurements in soft tissue, it is known that the backscatter signal should be dependent on the scatter structure, in this case the bone microstructure [12]. Reflection techniques, such as ultrasound critical reflectometry and backscatter, have recently been introduced for their diagnostic promise and clinical feasibility [8]. For instance, Chaffai *et al.* [13] found that the integrated backscatter coefficient (so-called broadband ultrasound backscatter or BUB) exhibits a strong linear correlation with BMD in 25 human calcaneus specimens. Recently, Padilla *et al.* [14] also investigated the relationship between BUB and BMD by using 37 human femoral specimens. Hakulinen *et al.* [15,16] demonstrated the feasibility of using BUB and integrated reflection coefficient (IRC) for predicting density and mechanical properties in bovine and human cancellous bone specimens. These *in vitro* studies suggest that BUB and IRC may have a potential as new indices, in addition to the existing QUS parameters of SOS and BUA for the diagnosis of osteoporosis [17].

In recent years, ultrasonic measurement along the axial direction of long bones has attracted the attention of a number of researchers [18]. Axial transmission techniques use a pair of transducers to measure the ultrasonic velocity through a fixed distance of the cortical layer of the bone along its long axis and can be easily applied to a number of skeletal sites, including the radius, finger phalanges, tibia, and hand metacarpal because of its easy transducer setup [8]. Two commercial QUS devices using axial transmission techniques have been developed to measure various non-heel anatomical sites such as the Soundscan 2000 (Myriad Ultrasound Systems Ltd., Rehovot, Israel) and the Sunlight Omnisense (Sunlight Medical Corp., Rehovot, Israel) [1]. These systems mainly measure the ultrasonic velocity along the anteromedial cortical border of the mid-tibia and the wrist, thereby taking advantage of a site that is easily accessible in most individuals. The ultrasonic velocity obtained this way is claimed to reflect the whole bone strength (failure load), a property that is related to bone size, mass distribution, cortical thickness, internal architecture, density, and elastic properties of the bone [19]. The dependence on cortical thickness of ultrasonic velocity is predicted by the theory of wave propagation in linearly elastic, homogeneous, solid materials [20-22]. There should be further studies on the role of the overlying soft tissue to minimize errors in the velocity measurements [23].

III. Theoretical Approach

3.1. Ultrasonic wave propagation in bone

Interpretation of QUS measurements raises numerous problems because of the great complexity of the medium: bone is a porous, anisotropic, and heterogeneous medium. This interpretation is essential with a view to connect the QUS parameters with bone elasticity, microstructure and macrostructure, and density which are all determinant of bone strength [6]. However, the complexity of the theoretical approach depends on the type of bone being studied. In cortical bone, the wavelength at the typical frequency of 1 MHz is about 4 mm, which is much greater than the structural heterogeneities (osteons, Haversian canals, osteocytes lacunae, apatite crystals) [24]. At first approximation, ultrasound at this frequency propagates in cortical bone as it would do in an anisotropic homogeneous medium. It becomes then relatively feasible to define a minimum homogeneous volume characterized by its density and elastic constants, and knowing the

mode propagating (longitudinal or shear wave, surface wave, Lamb wave) to connect the propagation velocity to these characteristics.

The propagation of ultrasound in cortical bone specimens is relatively well understood [1]. At high frequencies, bulk wave propagation occurs and the velocity is directly related to the elastic coefficients of bone and the bone density. Therefore, velocity measurements are a very useful tool for quantifying elastic properties in vitro. The velocity dispersion is slight and there is pronounced frequency-dependent attenuation. Attempts to measure cortical sites using ultrasound in vivo are compromised in part by the irregular geometry of real bones and the presence of other tissues [18]. Problems are particularly acute for transverse measurements, but clinically useful information may still be obtained. Measurements of velocity using the axial and reflection methods offer most potential in terms of accurate acoustic measurements of cortical bone *in vivo*. In both cases, however, further theoretical and experimental studies are required to understand fully the influence of bone geometry and the relationship with bone material properties.

The acoustic modelization of cancellous bone is much more complex owing to its greater complexity [1]. Cancellous bone is a highly porous, anisotropic, heterogeneous medium composed of a solid matrix (mineralized collagen) of interconnected plates and rods (trabeculae) filled with marrow. Trabecular elements of average size ranging between 50 μm and 150 μm are separated by an average distance of 0.5 mm to 2 mm [25]. These characteristic distances are close to the wavelength (3 mm at 0.5 MHz) and the propagation medium cannot be regarded as homogeneous at the frequencies used. The development of models for ultrasonic wave propagation in cancellous bone has received relatively little attention in the literature [1]. This is unfortunate because the absence of such models leaves us blind to many of the mechanisms underlying the observed acoustic behavior and to ways in which the required physical properties of bone can better be deduced from ultrasonic measurements. Establishing such relations through a validated predictive model for ultrasonic wave propagation in bone would be a significant advance.

3.2. Theoretical models

The Biot model for elastic wave propagation in porous media has attracted the most attention with regard to modeling wave propagation in cancellous bone [26,27]. This application of the Biot model was reviewed by Haire and Langton [28]. The Biot model was originally applied to the analysis of ultrasound geophysical test data for porous rock samples and is now the most widely accepted theory for acoustic wave propagation in fluid-saturated porous media [29]. Recently, Wear *et al.* [30] successfully applied the Biot model to predict the dependence of phase velocity on porosity in human calcaneus samples *in vitro*. The greatest difficulty in the application of the Biot model is that it depends on a large number of input parameters that are not easily measured, including elastic and structural parameters [27].

As an alternative propagation model in cancellous bone, Strelitzki *et al.* [31] proposed a scattering model based on velocity fluctuations in a binary mixture (marrow fat and cortical matrix) to estimate the ultrasonic attenuation in cancellous bone. Nicholson *et al.* [32] also used this scattering model in cancellous bone to predict the relationship between BUA and porosity. One of the potential limitations in this approach is that absorption is not included in the model.

Hughes *et al.* [33] first adopted the stratified model consisting of periodically alternating parallel solid-fluid layers, based on a work by Schoenberg [34], to predict the angular dependence of phase velocities for the fast and the slow waves in bovine cancellous bone *in vitro*. Wear [35] successfully applied the stratified model to predict negative dispersion of phase velocity in human cancellous bone *in vitro*. This is a very interesting alternative approach to the Biot model for wave propagation in

porous media [36,37].

Roh and Yoon [38] proposed the modified Biot-Attenborough (MBA) model for acoustic wave propagation in fluid-saturated porous media such as cancellous bone and water-saturated sediments. Lee *et al.* [27,39] successfully applied the MBA model to predict the dependences of phase velocity and attenuation on frequency and porosity in bovine and human cancellous bones *in vitro*. The MBA model is based on separate treatments of the viscous and the thermal effects of the fluid since this simplifies the derivation according to Attenborough [40,41]. The Biot model has the merit of including the viscous effect of the interstitial fluid, but it does not take into account the thermal effect [26,27]. In contrast, the MBA model includes the thermal effect specified by an analytic solution and also allows for an elastic solid and fluid medium by means of a parametric fit [27,38].

Table 1. Input parameters of the Biot model and the MBA model for cancellous bone.

Parameter	Biot model	MBA model
Density of solid (ρ_s)	1800 kg/m^3	1800 kg/m^3
Compressional speed of solid (c_s)		2500 m/s
Shear speed of solid (c_{sh})		
Young 's modulus of solid (E_s)	8.3 GPa	
Poisson 's ratio of solid (v_s)	0.3	
Poisson 's ratio of frame (v_b)	0.23	
Density of fluid (ρ_f)	1000 kg/m^3	1000 kg/m^3
Compressional speed of fluid (c_f)		1483 m/s
Bulk modulus of fluid (B_f)	2.2 GPa	
Viscosity of fluid (η)	0.001 Pa s	
Kinematic viscosity of fluid (ν)		110^{-6} m^2/s
Specific heat ratio of fluid (γ)		1.004
Prandtl number of fluid (N_{pr})		7
Permeability (k)	510^{-9} m^{-2}	
Variable (r)	0.25	
Frequency (f)	0.5 MHz	0.5 MHz
Porosity (β)	Variable	Variable
Pore radius (a)	Depend on β	0.5 mm
Tortuosity (α)	Depend on β	1
Exponent (n)	1.75	
Boundary condition parameter (s_1)		1.5
Phase velocity parameter (s_2)		1.23

3.3. Relationship between phase velocity and porosity in cancellous bone

In this section, the relationship between phase velocity and porosity in cancellous bone predicted from the Biot model and the MBA model are briefly summarized. Figure 1 shows the phase velocities at 0.5 MHz as a function of porosity predicted from the Biot model and the MBA model with the input parameters listed in Table 1 [27]. The experimental data for the 53 human calcaneus samples (with porosities from 86 % to 98 %) in the figure were taken from Wear *et al.* [30]. The 23 circles denote the samples for which porosity was directly measured by using *micro computed tomography* (*micro* CT). The 30 asterisks denote the samples for which porosity was estimated from DEXA measurements. The phase velocity at 0.5 MHz in all 53 bone samples was measured in a water tank using a pair of broadband, focused (focal length = 1.5 in.) transducers with a diameter of 1 in. and a center frequency of 0.5 MHz [30]. It can be found that the model predictions agree reasonably well with the experimental data, even if the data are limited to a narrow range of porosities (from 86 % to 98 %).

In the Biot model, the exponent n of the power law for the elastic moduli is a fitting parameter, which is optimized by curve fitting to the experimental data of phase velocity as a function of porosity [27,30]. As seen in Figure 1, the Biot model is well fitted to the experimental data with an optimized exponent of n=1.75 (Table 1). All of the additional input parameters of the Biot model were taken from Wear *et al.* [30]. In the MBA model, the parameter S_2 is the phase velocity parameter representing the form of the phase velocity curve as a function of porosity. It has a value less than unity if this curve is convex. Its value is larger than unity if the phase velocity curve is concave and is equal to unity if it is linear

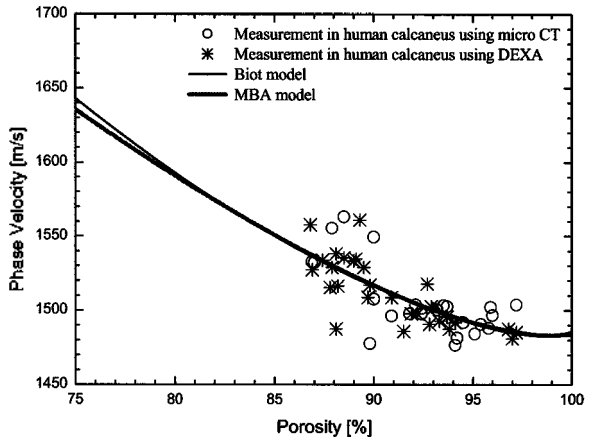

Fig. 1. Phase velocities at 0.5 MHz as a function of porosity predicted from the Biot model and the MBA model with the input parameters listed in Table 1. The experimental data for the 53 human calcaneus samples (with porosities from 86 % to 98 %) in the figure were taken from Wear et al. [30].

[38]. As with n, S_2 can also be optimized by curve fitting to the experimental data of phase velocity as a function of porosity. The value of S_2 obtained by curve fitting to the data for all 53 samples was 1.23 (Table 1). The values of the common input parameters of the MBA model were taken by our previous work [27]. As shown in Figure 1, a good agreement can be found between the predictions of the Biot model and the MBA model. This modeling effort is relevant to the use of QUS in the diagnosis of osteoporosis because SOS is negatively correlated to the fracture risk of bone, and also advances our understanding of the relationship between phase velocity and porosity in cancellous bone [37].

IV. Conclusions

The development of QUS technologies for the diagnosis of osteoporosis has advanced swiftly during the past 25 years [46]. New devices are being introduced and intensive multifaceted research continues in many areas of QUS technologies [6]. One of the most important limitations of QUS devices in clinical practice is their application to peripheral skeleton sites only. The risk of fracture is best predicted by analyzing the site where the fracture occurs. So far, no practical QUS methods have been developed at the most important fracture sites, such as the spine or the femur. This may be due to the fact that these central skeletal sites exhibit more complex geometries and are surrounded by more intervening soft tissue than peripheral sites. Meanwhile, previous *in vitro* studies on the relationships between QUS parameters and BMD at human proximal femur showed the feasibility of direct QUS measurements at the femur for *in vivo* fracture risk assessment [42-44]. Based on these promising results, an ultrasound device for *in vivo* measurements of QUS parameters at the human proximal femur was recently developed [45]. However, there is still room for improvements for the scanning technique and the data evaluation methods to enhance the potential of the new method for the assessment of osteoporosis. In conclusion, QUS technology has tremendous potential for further improvement and refinement. It may eventually be possible to develop a truly noninvasive method that will provide information on material or structural properties other than density, and ultimately on osteoporotic fracture risk.

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