

## Perspectives

# Ultrasound Assessment of Bone

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### INTRODUCTION

**T**HE CLINICAL MANAGEMENT of osteoporosis relies heavily on the use of bone mass measurements. To this end, several safe, precise, and accurate methods have been developed. All of these use some form of ionizing radiation, and the measurement obtained is a reading of the attenuation of a beam of energy as it passes through bone and soft tissues. Although bone mass shows a high correlation with bone strength, as much as 25–30% of the observed variation in bone strength may be due to the cumulative and synergistic effects of other factors, such as bone microstructure, architecture, and state of remodeling.<sup>(1,2)</sup> Bone mass measurements are incapable of measuring directly the effects of any of these factors on bone. In particular, a measure of the biomechanical competence of the skeleton cannot be obtained using these techniques. To determine how bone will respond to mechanical loads, the risk that a particular bone will fracture, and how the skeleton will be altered by a specific drug treatment, a noninvasive method for assessing bone integrity is needed. The use of acoustic energy in the form of an ultrasound wave has been suggested as possibly contributing to the achievement of these goals.

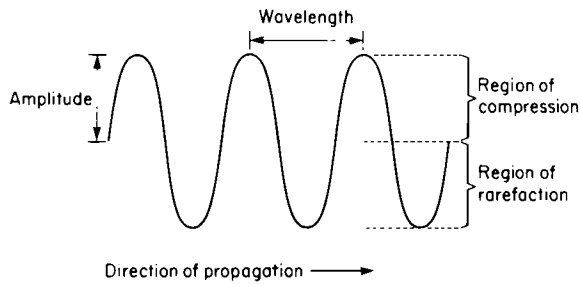
As a mechanical wave, ultrasound may have the ability to provide information on several properties of bone since it interacts with bone in a fundamentally different way compared with ionizing electromagnetic radiation. This, combined with the fact that ultrasound involves no radiation and is relatively simple to implement and process, accounts for the widespread interest it has received recently. Stated simply, ultrasound uses sound energy and photon absorptiometry, x-ray absorptiometry, and quantitative computed tomography use the energy of ionizing electromagnetic radiation. Like bone densitometry, ultrasound can be used to measure the attenuation of an energy (sound) wave as it passes through bone. However, what distinguishes ultrasound from bone densitometry is the potential for sound to be modified by bone's structure, composition, and mass in such a way as to provide additional

information about the tissue. The extent to which this new type of information can be related to the mechanical competence of the skeleton remains to be fully elucidated. It should be borne in mind, however, that there is still an incomplete understanding of the relationship between the in vitro or in vivo measures of the biomechanical properties of bone and the probability that a person will sustain a fracture. This fact alone may ultimately limit the ability of any technique that measures some physical property of the skeleton to predict a clinical outcome.

This article is a review of the fundamentals of ultrasound as it may be applied to the noninvasive assessment of bone. First, a brief description of ultrasound theory is presented; this includes definitions of some of the more commonly used terms. Since different investigators have employed different sets of nomenclature to describe the same or similar phenomena, we attempt to identify these redundancies and clarify areas of confusion. In addition we explain why specific anatomic sites, such as the calcaneus (also known as os calcis), radius, tibia, and patella, have been selected for analysis as opposed to the spine. Finally, we summarize the present state of the art by reviewing published literature and try to identify some of the more important questions that remain to be answered regarding the present limitations and future development of this technology.

### BASIC ULTRASOUND THEORY

Sound, whether it be ultrasound or audible sound, results from a mechanical disturbance in a medium such that each particle in the medium exhibits oscillatory movements. As a result of this disturbance a wave is propagated, and it is characterized by the areas of compression and rarefaction it produces (Fig. 1). The parameters of the wave can be defined by velocity  $c$ , frequency  $f$ , wavelength  $\lambda$ , and amplitude. The frequency of the wave defines the number of cycles per second at which the particles in the medium vibrate. The unit used to express frequency is the hertz (Hz). Wavelength can be described as the distance between the points of equivalent compression or rarefac-



**FIG. 1.** An ultrasound wave showing alternating regions of compression and rarefaction at a single instant in time.

tion in the medium at a particular instant in time. Frequency and wavelength are related to each other by the velocity of the sound wave, and this is given by the equation

$$c = \lambda f$$

Amplitude defines the height of the wave, and it is an indication of the intensity of the compression or rarefaction. Thus, in audible sound, a disturbance is created by the movement of molecules in air and this mechanical disturbance is detected by the organs of the inner ear. The amplitude of the wave determines how loud the sound is perceived to be.

Ultrasound is a mechanical sound wave consisting of frequencies above the range of human hearing (> 20 kHz). When an ultrasound wave is propagated through a medium, such as a biologic tissue, it produces regions of temporary compression and rarefaction in the tissue. When the oscillatory motion of the particles in the tissue is parallel to the direction of the wave, the mode of ultrasound propagation is said to be longitudinal. This is the most common mode by which ultrasound travels through tissues. When particle motion becomes perpendicular to the motion of the wave, a shear wave is produced. Liquid media can only support longitudinal waves; however, solids can support both longitudinal and shear wave types. Shear waves and longitudinal waves propagate within or through a medium. It is also possible to have waves that propagate along an interface between two materials, such as muscle and bone; these waves are known as surface or Rayleigh waves. In this case the particles of the medium execute an elliptical trajectory.<sup>(3)</sup> In complex heterogeneous materials like bone, ultrasound waves are generally mixed mode, thus increasing the complexity of the analysis and experimental investigations.

The generation of an ultrasound wave is most often accomplished by a piezoelectric transducer. This transducer utilizes a special material, often a ceramic, and is used to convert an electrical signal into a mechanical vibration. For example, by placing the transducer in physical contact with the surface of the skin, an ultrasound wave can be propagated through the underlying tissue. This condition constitutes a major difference between the use of ultrasound and bone densitometry techniques in that ultrasound requires actual contact between the measuring device and the anatomic part to be studied. Ultrasound waves are almost totally reflected at interfaces with air.

Thus, for example, ultrasound cannot be used in the same mode as dual-energy x-ray absorptiometry or photon absorptiometry of the thoracic or lumbar vertebrae since air in the lung or bowel would lead to a complete obliteration of the ultrasound signal. To assess ultrasonically bone in the vertebrae, it would be necessary for the transducer to make nearly direct contact with the bodies of vertebrae. At present, this is not possible and thus only anatomically accessible sites, such as the calcaneus, patella, radius, and tibia, which have minimal amounts of soft tissue covering them, can be studied. (Note: The spinous processes of the vertebrae are accessible to an ultrasound transducer, but since the wave would have to travel through the posterior elements of the spine before reaching the vertebral body, the ability to make accurate ultrasound measurements is not possible.)

The analysis of a tissue or medium using ultrasound is referred to as interrogation. Two basic approaches for ultrasonically interrogating materials exist. The first uses a single transducer that acts as both transmitter and receiver. This is known as the reflection mode and it is the method used to produce current medical ultrasound images. In this mode, a portion of the ultrasound signal is reflected back to the transducer whenever a change in the acoustic properties of the media occurs (Fig. 2). An example of this phenomenon takes place at the interface between soft tissue and bone.

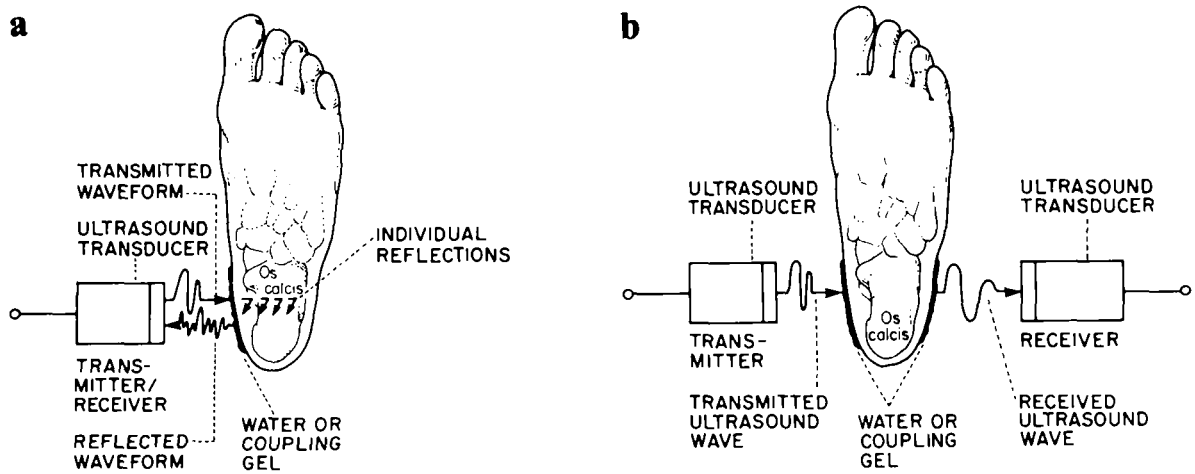
The alternative approach for tissue analysis uses two transducers, one acting as transmitter and the other as a receiver of the ultrasound wave. This method is known as the transmission mode. In this approach, the acoustic properties of the tissue can be obtained by comparing the received signal with a standard or reference waveform (Fig. 2). Each approach is best suited to specific applications. As noted, the reflection mode is most often used for soft tissue imaging and is simpler to implement in that it requires only a single transducer. The transmission mode requires two transducers, as well as access to both sides of the interrogated tissue.

## TISSUE CHARACTERIZATION BY ULTRASOUND

The ability of an ultrasound wave to provide information about the medium (tissue) through which it is being propagated depends on the way by which the wave is altered by the medium. Two principal types of alteration can occur: (1) the medium can alter the velocity of the wave, and (2) the medium can reduce the amount of energy transmitted and thereby attenuate the wave. Numerous reports have used a variety of terms and/or methods to describe these two alterations. At present there is no convention for the use of these terms.

### *Tissue alteration of ultrasound velocity*

The velocity of an ultrasound wave depends on the properties of the medium through which it is propagating and its mode of propagation. Longitudinal waves are generally



**FIG. 2.** Techniques for interrogating a tissue ultrasonically. (a) In reflection or pulse-echo mode, the same transducer serves as both transmitter and receiver. (b) In transmission mode, two transducers are used, one for transmitting the ultrasound wave and the other for receiving the signal after it has propagated through the tissue.

faster than shear waves, and these are faster than surface waves. A material whose cross section is small in relation to the ultrasound wavelength generally yields a lower velocity of ultrasound than would be obtained if the cross section were larger. Thus, for example, a person with a large os calcis may show a different value for ultrasound velocity even though bone density and quality may be equivalent to that of a person with a smaller os calcis. Complex materials like bone can support many propagation modes, and to complicate matters further, conversion from one mode to another can also occur. The ability of these confounding effects to alter ultrasound measurements is significant, and an awareness of the potential problems is critical when employing this technique in present clinical settings.

The velocity of ultrasound can be classified into one of two types, phase and group. *Phase velocity* refers to the velocity of a wave that travels through a medium at a single frequency. *Group velocity* is a term used to describe the velocity of a wave packet or pulse that consists of a finite number of frequencies. Group velocity is the quantity most often reported since pulse measurements are generally more easy to obtain. For certain media, such as water, the phase and group velocities are essentially equivalent. Media for which the phase or group velocities are not equivalent are known as dispersive. Bone is an example of a dispersive medium, and trabecular bone is significantly more dispersive than compact bone.<sup>(4,5)</sup> Since several investigators have utilized phase or group velocities in the assessment of bone (see later), it is important that this distinction be recognized. Furthermore, for dispersive materials like bone, both the phase and group velocities are frequency dependent. Therefore, different values are obtained depending on the frequency of the ultrasound waveform.

Ultrasound velocity can be analytically related to certain specific biomechanical properties. At present, it is possible to relate ultrasound velocity to the elastic modulus  $E$  and

compressive strength  $S_u$  of a material. [Note: "Elastic modulus" and "Young's modulus" are terms that describe a material property of a tissue. This property is related to a bone's stiffness. Compressive strength is also a material property of a tissue, and it is related to a bone's load-carrying capacity. Material properties (e.g., elastic modulus and compressive strength) describe mechanical properties of a tissue that are independent of geometry and architecture. Structural properties (e.g., stiffness and load-carrying capacity) are mechanical properties that depend on the material properties of a tissue as well as its geometry and architecture.<sup>(6)</sup>]

When the ultrasound wavelength is large with respect to the cross-sectional area of the tissue and for homogeneous and nondispersive media, the relationship between elastic modulus and the ultrasound velocity is given by the equation

$$c = (E/\rho)^{1/2}$$

where  $\rho$  is the density of the material and  $c$  is the longitudinal velocity (in this case, the phase and group velocities are equivalent).<sup>(3)</sup> This equation does not apply to heterogeneous, anisotropic (i.e., where the biomechanical properties are a function of the spatial direction), and dispersive materials like bone. In this case, no general closed form solutions exist. Thus, this equation is often used to provide first-order estimates of the biomechanical properties of bone, as follows. Since for bone,

$$E \approx k \rho^\alpha$$

where  $k$  is a constant, equations can be derived in which the velocity is related to  $E$  and  $\rho$ :

$$E \approx k_1 c^{2\alpha/(\alpha - 1)}$$

and

$$\rho \approx k_2 c^{2/(\alpha - 1)}$$

where  $k_1$  and  $k_2$  are constants that depend on  $k$  and  $\alpha$ . (Note: Controversy exists as to the power function of  $\alpha$  in this equation. Carter and Hayes<sup>(7)</sup> determined that  $\alpha = 2$ ; Rice et al.<sup>(8)</sup> reported that  $\alpha = 3$ . Independently of this argument, the form of the equation  $E \approx kp^\alpha$  remains the same.)

According to classic relationships developed in biomechanical stress-strain curves, the elastic modulus of bone is proportional to its compressive strength.<sup>(8)</sup> Therefore, using these relationships, values for the ultimate compressive strength of bone can be derived. Using another constant  $k_3$ , the ultimate compressive strength  $S_u$  is related to the ultrasound velocity by the equation

$$S_u \approx k_3 c^{2\alpha/(\alpha-1)}$$

Velocity may be measured in either reflection or transmission mode, and the choice depends primarily on the material being measured and the equipment available. In both cases, an estimate of the bone tissue thickness is necessary to relate the ultrasound measurements to wave velocity. It should be noted that there is an extremely complex and substantially unknown relationship between ultrasound velocity and the physical and biomechanical properties of heterogeneous materials like bone. Nonetheless, several studies have demonstrated significant correlations between velocity and bone density and strength, as is discussed subsequently.

#### *Tissue attenuation of an ultrasound wave*

The attenuation of an ultrasound wave occurs by a reduction in its amplitude and results in a loss of acoustic energy. Two primary mechanisms can produce this attenuation: scattering and absorption. In scattering, the amplitude of the propagating wave is reduced because the energy has been redistributed in one or more directions. In this case, the amount of scattering depends on both the wavelength of the ultrasound signal used and the specific acoustic properties of the medium. A simple type of scattering, backscattering, occurs when a portion of a transmitted ultrasound wave is reflected back toward the source. As noted, this happens when an ultrasound wave propagates from one medium to another (e.g., soft tissue to bone). More complex scattering can arise in a material with acoustic inhomogeneities. Bone is an excellent example of an acoustically inhomogeneous material because it is composed of a cortical shell and a trabecular framework and is filled with a liquid-like material, bone marrow.

When an ultrasound wave undergoes absorption, a portion of the energy of the propagating wave is converted directly into heat. This conversion is an extremely complex process and depends on the molecular composition of the material and the frequency of the ultrasound wave. Absorption results when the density fluctuations within a medium are out of phase with the pressure fluctuations. This leads to energy loss through phase cancellation and so-called relaxation mechanisms.<sup>(9)</sup> In general, absorption increases with increasing ultrasound wave frequency.

In sum, the loss of ultrasound energy in a tissue consists of the individual contributions from scattering and absorption and is quantitated by the equation

$$\alpha = \alpha_s + \alpha_a$$

where  $\alpha$  is the attenuation coefficient and  $\alpha_s$  and  $\alpha_a$  are the scattering and absorption coefficients of the medium, respectively. Attenuation is usually expressed in the units nepers (N) or decibels (dB). A medium that has an attenuation of 1 neper reduces the amplitude of an ultrasound wave to approximately 37% of its initial value. A medium with an attenuation of 3 nepers reduces the amplitude to approximately 5%. One neper is equivalent to approximately 8.65 decibels.

The attenuation coefficient  $\alpha$  of a medium like bone is related to its thickness  $d$ . This parameter can be used to derive the specific attenuation  $\mu$  according to the equation

$$\mu = \alpha/d$$

Specific attenuation is usually expressed in nepers/cm or dB/cm.

As noted, ultrasound attenuation is a function of frequency. For many materials, such as plastics and biologic soft tissues, this relationship is linear over a wide frequency range. In these cases, the attenuation coefficient  $\alpha$  is characterized by the slope  $\alpha_1$  of the regression line and is expressed in the terms nepers per megahertz (np/MHz) or decibels per megahertz (dB/MHz). Similarly, the specific attenuation  $\mu$  is characterized by the slope  $\alpha_1$  of the corresponding regression line and is expressed in nepers/cm-MHz or dB/cm-MHz. When the material's attenuation cannot be characterized by a linear dependence on frequency, polynomial functions (including perhaps nonintegral exponents) may be necessary to provide a reasonably good approximation of the relationship. Bone is an example of such a material; its linear dependence on frequency occurs over a relatively limited frequency range.

Attenuation can be measured both in reflection and transmission modes. For materials with high attenuation (e.g., bone), the transmission mode is more practical since the acoustic wave must pass through the material only once. It is important to point out also that ultrasound measurements on heterogeneous materials like bone engender a host of practical problems. For example, the irregular geometry of bone can produce inaccurate readings of attenuation through phase cancellation effects.<sup>(9)</sup> There can also be a large variation in measured attenuation depending on the specific region of bone interrogated by the ultrasound wave. Soft tissue surrounding the bone can also affect both ultrasound attenuation and velocity estimates. Moreover, in contrast to velocity, no theoretical relationship between a material's ultrasound attenuation and elastic modulus has been established. Finally, as noted earlier, there remains a lack of empirical knowledge relating ultrasound attenuation in bone to its specific biomechanical properties, that is, density, architecture, and strength.

In summary, ultrasound assessment of bone relies primarily on the measurement of two basic characteristics: the velocity and attenuation of the ultrasound wave. These features are in general, frequency dependent. Ultrasound characterization of bone is based on the hypothesis that bone in different biomechanical states has different values for velocity and attenuation. However, because of the heterogeneous, anisotropic, and complex physical properties of bone, the applicability of these measurements to the

clinical setting requires more research. The development of unique and quantitative relationships between ultrasound velocity and attenuation, on the one hand, and the physical properties of bone and fracture risk, on the other, constitutes the critical research goal for this technology.

## REVIEW OF PREVIOUS STUDIES

Because of the anatomic considerations just outlined, the most accessible sites for ultrasound measurement to date have been the calcaneus and patella and, to a lesser extent, the radius, tibia, and phalanges. Using these sites, clinical studies have been performed and certain conclusions have been drawn regarding the utility of the information derived. As noted, there are essentially two approaches to ultrasound assessment of bone: the first uses ultrasound velocity and the second uses the frequency-dependent attenuation. Studies thus far have concentrated on one of these two approaches; very few have attempted to combine the information derived from both. Each approach has its own set of advantages and disadvantages. In general, velocity is easier to measure and results in greater precision. Measurement of attenuation usually requires more complex hardware and results in less precise data. To what extent each of these ultrasound parameters contains independent and important information on bone biomechanics is not yet understood.

### *Velocity-based bone assessment*

Preclinical studies in which ultrasound has been used to assess certain physical qualities of bone have been conducted in both in vitro and in vivo settings. These data provide information on the relationship between ultrasound velocity and some biomechanical property but do not necessarily identify the presence of osteoporosis or predict fracture risk.

Using the transmission mode of ultrasound in human and bovine cortical bone specimens, Abdenshein and Hyatt,<sup>(10)</sup> as early as 1970, found a high correlation between mechanically determined and ultrasonically determined elastic moduli. These findings were later reproduced by Ashman et al., who studied the elastic properties of cortical bone using a more defined continuous wave technique.<sup>(11)</sup> More recent studies on trabecular bone samples from human and bovine subjects have shown correlations of ultrasound velocity with ultimate strength ranging from 0.71 to 0.75.<sup>(4,12)</sup> Since these studies actually examined whole trabecular samples, not individual trabeculae, the term "ultimate strength" should more properly be designated "load-carrying capacity," and as such, the data suggest that ultrasound velocity can be used to predict the occurrence of a fracture in vitro at a given trabecular site.<sup>(4,12)</sup>

In animal studies, it has been possible to assess the interaction between a physiologic event or manipulation and a physical outcome measured by ultrasound velocity assessment. Using a sheep Achilles tenotomy model to mimic disuse, Rubin et al. studied the changes in ultrasound transmission through the calcaneus over a 12 week pe-

riod.<sup>(13)</sup> They noted a 10.2% decline in ultrasound velocity in the experimental limb, and this was associated with a 21% reduction in trabecular bone volume. Although these data do not identify the sensitivity of the ultrasound technique, they show that ultrasound velocity assessment can be used to identify an osteoporotic change. More recently, McCarthy et al.<sup>(14)</sup> studied the relationship between ultrasound velocity and the effects of specimen orientation, density, porosity, and temperature in equine cortical bone and showed a positive linear correlation between ultrasound velocity and bone specific gravity and an inverse relationship with porosity.<sup>(14)</sup> To determine the ability of ultrasound to detect a positive change in bone mass, Lees and Hanson examined the relationship between ultrasound velocity in the rabbit femora before and after sodium fluoride treatment.<sup>(15)</sup> They reported an "optimum dose" for fluoride administration based upon the ability to calculate the elastic modulus of bone. However, since it is still unknown how an increase in bone mass as a result of fluoride treatment is related to the improvement in the mechanical properties of bone or the ability of bone to resist fracture, it is not apparent from this study that the data obtained from ultrasound velocity assessments can necessarily be used to improve our understanding of the relationship between bone mass and fracture risk.

Several clinical studies utilizing velocity-based ultrasound transmission mode techniques have been performed, and these have provided some interesting and useful information regarding the potential use of ultrasound to identify patients with osteoporosis and possibly to predict fracture risk. As noted, there has been no convention on the use of terms, and therefore it is important for the reader to understand that a plethora of synonymous nomenclatures, such as speed of sound (SOS), velocity of sound, apparent velocity of ultrasound, and ultrasound transmission velocity, all refer to the same ultrasound measurement. Two of the most important studies in this area have been conducted by Heaney et al.<sup>(16)</sup> and Rubin et al.<sup>(17)</sup> In the study by Heaney et al., ultrasound velocity measurements made across the patella of osteoporotic patients (defined by the presence of atraumatic vertebral compression deformity) were 3–4% lower than in normal controls. By assessing fracture incidence, these investigators were able to show that women who had ultrasound velocity measurements below 1825 m/s were approximately six times more likely to have sustained one or more vertebral fractures than women with velocities above this level. In the study by Rubin et al.,<sup>(17)</sup> a carefully controlled physical exercise program was employed and longitudinal group velocity measurements were made at the patella and tibia. By simultaneously measuring the mechanical properties of bone, the study demonstrated the ability of an ultrasound velocity measurement to predict an increase in a mechanical or physical property of bone as a result of a chronic osteogenic stimulus. However, since no other physical measurement was used with which to correlate the ultrasound findings, it is unknown how accurate these measurements were in assessing the degree of bone mass increase or improvement in mechanical properties.

Two studies using sound velocity were performed in the upper extremity. One was unable to show a statistically sig-

nificant difference in ultrasound transmission across the middle phalanx between control subjects and patients who had undergone hemodialysis for from 1 to 7 weeks.<sup>(18)</sup> The other study examined the radius and claimed that ultrasound velocity is a better discriminator than single-photon absorptiometry for assessing normal versus osteoporotic bone.<sup>(19)</sup> However, the authors of this study provided no quantitative information with which to justify this claim.

Only one published report has tested a clinical effect using a reflection measurement for ultrasound velocity. In this study, transilial bone biopsies from 16 patients with osteoporosis and vertebral compression fractures were interrogated, before and after 2 years of intermittent slow-release sodium fluoride therapy.<sup>(20)</sup> For the fluoride treatment group, the mean fractional change in velocity increased 6.1%, with a total of 13 patients (81%) demonstrating statistically significant higher velocities after treatment. The technique of velocity measurement employed in this study allowed assessment of the material properties of individual trabeculae and was shown to be independent of a concomitant 5.3% increase in lumbar spine bone mass. Thus, this technique is distinct from those used in other studies that have assessed only macroscopic or bulk material ultrasound velocities.

#### *Attenuation-based bone assessment*

The second major group of studies on ultrasound assessment of bone have used ultrasound attenuation to characterize bone tissue. Many investigators have adopted the term "broadband ultrasound attenuation" (BUA) to denote the slope of the ultrasound attenuation curve. (This corresponds to  $\alpha_1$  or  $\mu_1$  defined in the previous section.) BUA is usually not normalized to tissue thickness and is therefore reported in the units dB/MHz ( $\alpha_1$ ). Thus, it also reflects overall bone geometry. Measured values of BUA depend on the frequency range over which it is evaluated since for bone, the slope (BUA) is known to be frequency dependent.<sup>(21)</sup>

In vitro experiments using BUA have compared bone ultrasound measurements to densitometric findings. McKelvie et al. compared quantitative computed tomography (QCT) to the ultrasound attenuation slope in the human calcaneus and showed a correlation of  $r = 0.92$ .<sup>(22)</sup> Similarly, McCloskey and coworkers examined the relationship between the ultrasound attenuation slope in the os calcis and both bone mineral density and physical density.<sup>(23)</sup> The slope was found to be highly correlated with both QCT ( $r = 0.80$ ,  $P < 0.0001$ ) and physical density ( $r = 0.85$ ,  $P < 0.001$ ). These investigators noted that the correlation between physical density and ultrasound attenuation slope was independent of QCT, a finding that suggests that ultrasound has the ability to differentiate between the mineral density and the physical density properties of human bone specimens.

Clinical studies using BUA have also compared ultrasound estimates to bone densitometry measurements. In a review of 44 subjects, the ultrasound attenuation slope of the os calcis was shown to be highly correlated ( $r = 0.80$ ,  $p < 0.001$ ) with single-photon absorptiometry (SPA) of

the distal forearm.<sup>(24)</sup> In contrast to these findings, two studies done in normal and osteoporotic women suggested that ultrasound attenuation slopes measured in the os calcis cannot be used to predict reliably trabecular bone density of the spine (measured by QCT) or of the distal radius (measured by either QCT or SPA).<sup>(25,26)</sup> Both these investigations reported standard error estimates of greater than 39%. Similarly Agren et al. studied 17 normal and 41 osteoporotic subjects and found a significant decrease in the ultrasound attenuation slope in the osteoporotic patients.<sup>(27)</sup> At a BUA value of 63 dB/MHz, the sensitivity and specificity of the measurements were only of the order of 76%. However, when BUA of the os calcis was compared to dual-photon absorptiometry and QCT of the spine in patients with Gaucher's disease, BUA was found to be highly correlated with QCT ( $r^2 = 0.85$ ,  $p < 0.01$ ) and less well correlated with DPA ( $r^2 = 0.47$ ,  $p < 0.05$ ).<sup>(28)</sup>

The wide range of discrepancies in these reports is probably due to the specific differences in the ultrasound measurement techniques. Many factors may be responsible, including transducer diameter and nominal frequency, transducer separation distance, and the frequency range used to evaluate the differential specific attenuation. Also of importance is the means by which the transducers are coupled to the body (e.g., direct contact or through a water bath). These and other factors can produce significant differences in reported ultrasound attenuation and velocity values.

Of great interest is the use of ultrasound to potentially improve on the ability of noninvasive diagnostic tools to predict fracture risk. In a study of 60 women, Langton et al. showed that those who had experienced a hip fracture within 4 weeks of the BUA measurement had a lower attenuation slope than women who had no history of fracture.<sup>(29)</sup> In addition, these investigators reported a significant decrease in the attenuation slope in relation to age. More recently, Miller and Porter measured ultrasound attenuation in 840 women over the age of 65 years, 32 of whom had sustained a fracture of the proximal femur during the study period.<sup>(30)</sup> The mean ultrasound attenuation slope was significantly lower in the fracture compared to the nonfracture group. Similar results were reported by Baran et al., who studied ultrasound attenuation of the os calcis in patients with hip fractures and those with established osteoporosis but no history of hip fracture.<sup>(31)</sup> At ultrasound values of 50 dB/MHz, this study showed sensitivities and specificities of the order of 80% for identifying hip fracture patients.

These attenuation studies, like the velocity studies discussed previously, showed significant correlations between bone density and/or incidence of fracture in osteoporotic patients. However, studies that measure combined ultrasound attenuation and velocity may be of greater value.

#### *Combined studies*

Only a limited number of studies have employed both ultrasound attenuation and velocity methods to assess bone. Two clinical investigations have reported measure-

ments of ultrasound attenuation and approximate group velocity in the same subjects.<sup>(32,33)</sup> These authors reported that correlation coefficients between SPA and ultrasound attenuation slopes and velocities in the os calcis were 0.53 and 0.72, respectively. These relatively poor correlations may be because a focused transducer was used in the measurements that interrogated a small and highly variable portion of the os calcis. A recent clinical study combining both BUA and SOS in the os calcis derived a third parameter, "stiffness."<sup>(34)</sup> It is important to note that the term "stiffness" as utilized here has no relation to the true biomechanical term as defined in engineering texts or as discussed earlier in this article. These investigators showed that, in 23 normal and 18 osteoporotic women, BUA, SOS, and stiffness were significantly lower in the osteoporotic subjects ( $p < 0.001$ ). The magnitude of the difference in ultrasound measurements was greatest in stiffness (17%), with a  $Z$  score of 1.2 [ $Z$  score is the distance from the mean value in numbers of standard deviations,  $Z = (x - \mu)/\sigma$ , where  $x$  is the individual measurement,  $\mu$  is the mean, and  $\sigma$  is the standard deviation of the group]. There is no indication that the derived parameter known as stiffness represents an optimal or nearly optimal combination of the ultrasound attenuation and velocity.

An important and fundamental *in vitro* study to determine the ability of BUA and ultrasound group velocity to detect alterations in bone mineralization was recently conducted on bovine bone samples.<sup>(35)</sup> Using controlled nitric acid attack to sequentially demineralize bone, BUA and SOS were shown to be highly correlated ( $r$  values between 0.84 and 0.99) with bone physical density. However, these investigators noted that the accuracy of the measurements at higher frequencies may have been diminished as a result of the scattering effect of hydroxyapatite crystals on these types of sound waves. This suggests that inherent problems still exist in applying acoustic energy to complex material like bone. Similarly, another *in vitro* study determined both the attenuation and phase velocity of ultrasound over frequency ranges of 300 kHz to 3.0 MHz in cancellous bone from the human skull.<sup>(36)</sup> These authors concluded that the frequency dependence of ultrasound attenuation and phase velocity was caused principally by the scattering of sound by the blood- and fat-filled interstices of the bone compartment. To date, no studies have measured both frequency-dependent velocity and frequency-dependent attenuation *in vivo*. This is a question that needs to be addressed in subsequent investigations.

### FUTURE STUDIES

Several questions remain to be answered before ultrasound should be considered a practical clinical tool for bone assessment. This section delineates the major areas for future research and suggests some experiments that may address the more important issues.

A clear understanding of the quantitative relationship between ultrasound attenuation and velocity, on the one hand, and bone strength, density, and architecture, on the other, does not yet exist. Although prior reports have stud-

ied various aspects of the overall relationship, none have examined the collective interactions between these variables. This would help to determine, for example, which features of ultrasound are related to bone density per se, which reflect changes in architecture independent of density, and how these relate to specific biomechanical properties. It would be useful to carry out *in vitro* experiments in which bone density, architecture, and strength could be related simultaneously to measurements of ultrasound velocity and attenuation. These measurements should be performed in three orthogonal directions.

More information needs to be generated to understand the unique interaction between bone tissue and sound energy since bone interacts with sound in a fundamentally different way from many other materials. As noted, most studies report a constant value for the slope of the attenuation curve (BUA) and a single value for velocity. However, bone exhibits a much more complex behavior in relation to ultrasound in that the true ultrasound attenuation slopes and velocities are not constants.<sup>(4,36)</sup> It is important to quantitate this behavior and incorporate this additional information into the prediction of bone strength and density. In addition, since as bone mass changes, the individual components of bone may change their physical properties (for example, the change noted in crystal size when bone undergoes demineralization), the effects of these changes on ultrasound measurements must be determined.

Additional efforts should also be directed toward examining the influence of ultrasound frequency on the measured attenuation and velocity values. Until now, only a relatively small portion of the frequency spectrum has been used to interrogate bone tissue, typically 300–800 kHz. It is possible that significant structural information exists in the attenuation and velocity data at other frequency ranges, most notably the lower frequencies ranging from 50 to 300 kHz.

It is reasonable to think that information obtained from ultrasound measurements can be used to complement the information obtained from bone densitometry studies, particularly with regard to predicting fracture risk. Clinical studies to test this hypothesis are required.

Finally, it is critical that precision and accuracy data be established for any ultrasound device that is developed. This is a significant task since both velocity and attenuation measurements are dependent on the site of interrogation and each site may have its own unique set of problems associated with obtaining good reproducibility. High-precision estimates are at least partially dependent on the ability of the measurer to reposition the ultrasound transducers to the same location each time a measurement is made. This interactive component of current ultrasound technology must clearly be reduced, preferably eliminated, in favor of a more automated system.

### CONCLUSIONS

It is clear that a noninvasive method for assessing bone integrity and fracture risk could add substantially to our ability to gain critical information about the natural his-

tory of metabolic bone diseases and lead to new approaches for testing therapeutic interventions. Present-day bone densitometry techniques are very good at making accurate and reproducible estimates of bone mineral content, and these estimates are highly correlated with in vitro measurements of bone biomechanical properties. However, they are less useful in helping to predict which patients with low bone mass will sustain fractures and how certain pharmacologic agents may improve bone mass and reduce fracture risk. Ultrasound assessment of bone has been shown to provide another means of assessing bone mineral content and, to some unknown extent, may provide additional information that may be relevant to other aspects of bone quality, such as its geometry, architecture, and biomechanical properties. Preliminary studies already suggest that certain ultrasound measurements can be used to predict which patients with low bone mass are at risk for sustaining hip and vertebral fractures.<sup>(16,30,31)</sup> Although a substantial body of information has been generated with a variety of ultrasound measuring devices, several questions relating to the interpretation and relevance of these data must be resolved.

The time has come to develop standards and goals for ultrasound assessment of bone. Well-accepted nomenclatures must be established, and investigators must meet to exchange information to identify the relevant questions and the methods needed to answer them. The notion that acoustic energy can be used to provide new information about bone quality and integrity is very attractive. The extent to which this new information will impact positively on clinical practice awaits further investigation.

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