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Clinical Determination of Bone Quality: Is Ultrasound an Answer?

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Summary. Progress in clinical characterization of bone relies on developing a means to clinically assess *all* of the important determinants of bone quality, specifically, the intrinsic material properties of a bone (stiffness and brittleness) versus the macroscopic structural properties [apparent mass density (g/cc), structural shape and distribution of cortical mass, trabecular architecture, extent of unrepaired microdamage, and defects associated with the accelerated remodeling in early menopause]. Ultrasound devices currently measure parameters related to either of only two basic properties: bone ultrasound attenuation (BUA) or the apparent velocity of wave propagation (AVU). Theory and repeated corroboration in the laboratory have shown that the velocity of sound in solids such as bone has a quantitative relationship to the elastic modulus (or stiffness) and mass density. Although no comparable physical model exists for BUA, growing *in vitro* and *in vivo* empirical evidence shows a relationship to stiffness and mass density as well. Therefore, the question of ultrasound's ability to provide additional, clinically useful information about bone quality reduces to this: *Does bone quality depend significantly on bone stiffness and does stiffness depend on factors other than bone mass alone?* Clinical study results provide mounting evidence of ultrasound's abilities. (1) Numerous studies compare either velocity or BUA with BMC or BMD. The correlation coefficients vary widely between studies, even when repeated by the same investigators and laboratories. Two studies demonstrated this by comparing groups of subjects who are indistinguishable by BMD at the lumbar spine, but whose mean AVU readings are significantly different. (2) Multiple studies of AVU and BUA by different investigators have shown the ability of ultrasound to distinguish, as effectively as BMC or BMD, women with osteoporotic vertebral crush deformities from normal women. Prospective studies have shown that AVU and BUA each indicated risk of future osteoporotic fractures. In a population-based, randomized, cross-sectional study of men and women, AVU discriminated between groups of subjects who had suffered low trauma fractures versus those free of fracture. Such repeated clinical evidence of the ability of BUA and AVU to detect bone fragility provides mounting evidence that ultrasound measures a clinically relevant property of bone quality in addition to and distinct from bone mass.

Glossary

AVU: Apparent velocity of ultrasound transmission (meters/second) measured at the patella over the frequency range of 150–300 KHz [5, 6].

BMC: Bone mineral content, expressed in grams, obtained from a bone densitometer without normalizing for the area or volume over which the measurement was made.

BMD: BMC obtained by normalizing for width (grams/cm), area (grams/cm^2) or volume (grams/cc) over which the measurement was made.

BUA: Bone ultrasound attenuation (decibels/megahertz [db/MHz]) is the amount of ultrasound intensity lost during transmission through bone, derived from the slope of the approximately linear dependence of the attenuation coefficient on frequencies between 300 and 600 KHz [7, 8].

DPA: Dual photon absorptiometry measurement of BMC or areal BMD based on attenuation of X-rays emitted by a radioactive isotope at two different energy levels.

DXA: Dual energy X-ray absorptiometry measurement of BMC or areal BMD based on attenuation of X-rays produced by an X-ray tube, measured at two different energy levels.

SPA: Single photon absorptiometry measurement of BMC or grams/cm based on attenuation of X-rays emitted by a radioactive isotope at a single energy level.

QCT: Quantitative X-ray computed tomography measurement of BMC or volumetric BMD over a user-specifiable region of interest.

Key words: Ultrasound – Bone fragility – Osteoporosis – Fracture.

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Bone Quality and Bone Fragility

To date, there are no universally agreed upon definitions for these terms, nor is their relevance to health or the need for therapy fully understood. Growing interest in these measures arises from the need to characterize, prospectively, the ability of bone to withstand the daily rigors of normal use throughout life without elevated risk of spontaneous, low-trauma fracture.

Although osteoporosis results from a complex, incompletely understood set of physiological and biochemical conditions, the symptom is purely mechanical—a bone spontaneously fractures or permanently deforms (as with the vertebrae) without excessive trauma. The quality of bone—its ability to resist such mechanical failure—is a biomechanical property. Prevention of mechanical failures resulting from osteoporosis should benefit from early detection of deteriorating bone quality.

With the recent advances in X-ray technology, bone mineral content (BMC) and mass density (BMD) measurements have attained remarkable levels of precision and accuracy, with significant reductions in ionizing radiation exposure.

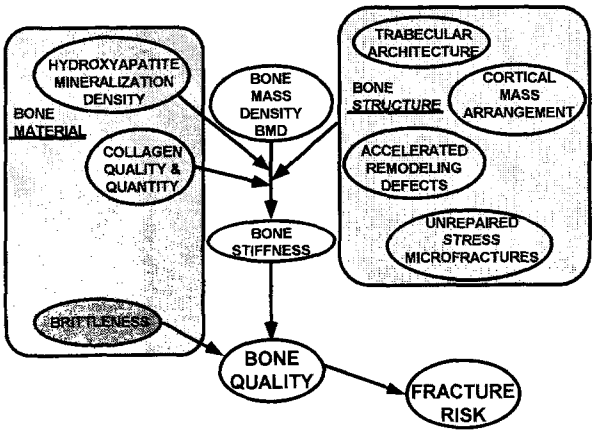

Fig. 1. Determinants of increased risk of low trauma fracture. Increased risk of low trauma fracture results from greater propensity to fall and diminished bone quality. Both the intrinsic properties of the hydroxyapatite and the macroscopic structural arrangement of this bony material determine the quality of the bone and its ability to withstand normal daily stresses without fracture or permanent deformation.

Densitometer performance has improved to the point where we can no longer attribute to measurement variance the inability of BMC and BMD readings to account completely for spontaneous mechanical failure [5, 6].

Therefore, further progress in clinical characterization of bone—and the ability of bone to resist permanent deformation or fracture—relies on improving our understanding of fundamental bone biomechanics and on developing a means to clinically assess *all* of the important determinants of bone quality. (Fig. 1). Specifically, we need to understand the relative importance of the intrinsic material properties of a bone (stiffness and brittleness) versus the macroscopic structural properties (apparent mass density (g/cc), structural shape and distribution of cortical mass, trabecular architecture, extent of unrepaired microdamage, and defects associated with the accelerated remodeling in early menopause [6].

Sound is a traveling mechanical vibration. As sound propagates, the mechanical properties of the medium progressively alter the shape, intensity, and speed of the propagating wave. By observing the differences between the wave transmitted into a bone and the wave after interacting with the bone, one can obtain information about the bone's mechanical properties, specifically, its stiffness and mass density.

Investigators have employed numerous means for measuring the effects of bone on the propagation of sound waves. Methods have ranged from mechanically vibrating the bone and measuring the resulting resonance [7–17], to measuring the amount of sound intensity lost in traveling through bone [3, 18–21], to measuring the speed with which sound travels through bone. The associated devices for *in vivo* use have shown vivid imagination but little overt similarity: calibrated hammers and microphones; vibrators and accelerometers; and ultrasound transducers mounted in water tanks, on elaborate scanning arms, or on digital calipers. Measurement sites have included, in humans, the tibia, ulna, radius, patella, calcaneous, and the digits; and in horses, the metacarpus and metatarsus. Each device has had its own complexities, precision, and accuracy, but all have shared a common attribute: all have provided measurements related to the stiffness and mass density of the bone.

These devices ultimately measure parameters related to either of only two basic properties: acoustic attenuation (loss of intensity due to scattering and conversion to heat within the bone) and wave propagation velocity. Based on long-standing theory and repeated corroboration in the laboratory, we know that the velocity of sound or flexural waves in solids such as bone has a quantitative relationship to the elastic modulus (or equivalently, the stiffness) and mass density [8, 9, 15, 22–27]. Although no comparable physical model exists for attenuation, a growing body of *in vitro* and *in vivo* empirical evidence shows a relationship to stiffness and mass density as well [4].

Therefore, as the vibration and ultrasound methods all yield information about bone stiffness, the question of sound's ability to provide additional, clinically useful information about bone quality reduces to this: *Does bone quality depend significantly on bone stiffness and does stiffness depend on factors other than bone mass alone?*

History of Bone Quality Assessment with Sound

This paper focuses on the history of bone assessment with vibration and ultrasound, and examines particular technologies and associated studies which have both shaped this emerging field and contributed to clinical assessment of bone quality. For more general summaries of bone assessment with ultrasound, refer to Antich et al. [28] and the review by Einhorn [6]. This history can be divided into five overlapping parts: (1) early *in vitro* studies of ultrasound velocity and attenuation to assess mechanical properties of human and animal bone [29–32]; (2) early attempts to assess bone clinically with prototype ultrasound devices either to detect osteoporosis with transmission velocity [22, 33, 34], or to monitor bone fracture healing with ultrasound [35–40]; (3) attempts over two decades to detect osteoporosis or monitor fracture healing using clinical devices to measure the mechanical response of bone to low frequency vibration [8, 9, 13, 17, 40, 41]; (4) recent, highly refined *in vitro* measurements of the mechanical properties of bone using ultrasound transmission velocity [23–27, 42, 43]; and (5) recently developed technologies to measure ultrasound velocity and attenuation in transmission—leading to the first commercially available devices and the first clinical studies to be repeated using similar devices in various laboratories worldwide: ultrasound attenuation and apparent velocity at the calcaneous [3, 18–21, 44, 45] and apparent velocity at the patella [1, 46, 47].

To prepare for the analysis to follow, it is helpful to first review pertinent aspects of the history and science of the bone vibration and bone ultrasound technologies.

Bone Vibration Technology

A direct application of technology from the field of nondestructive testing of materials has involved vibration of long bones [7–16]. Measurement of the mechanical response to artificially induced flexural vibrations has been used for decades to determine, for example, the integrity of rigid structures. As with bone velocity measurements, bone vibration analysis has the potential to yield a measure of a bone's ability to resist mechanical failure which is related to mass density and to stiffness.

In practice, the complex shape of even long bones such as the tibia, radius, or ulna causes highly complex mechanical response to vibration. A bone does not simply ring with a pure tone at a single frequency. Measurements of the response to vibrations over a range of frequencies, fit to a multiparameter physical model, can yield an estimate of the

bending stiffness of the bone [10, 14–17, 48]. In theory, such a model can account, at least in part, for the shape of the bone, damping (dulling of the resonance analogous to touching a ringing bell with your finger) due to soft tissue and the visco-elastic properties of the bone itself, the mass of the bone and its stiffness. Placement of the vibrator and sensor, overlying soft tissue, and any tension in overlying muscles can complicate attaining reproducible results [10, 13, 15, 48].

In vivo tests of vibration devices have yielded measurements that exhibit definite relationships to bone mass density, bone mineral content, stiffness, flexural strength, and breaking strength [7, 14, 16]. One of the more intriguing results comes from McCabe et al. [16] who showed that ulnar bending stiffness measured by mechanical vibration correlated with BMC and bone width in young females, but correlated only with BMC in older women. These results suggest a changing dependence of bone strength on bone mass versus other, nonmass-related structural properties of bone, as discussed below.

Ultrasound

Long before bone densitometry attained today's sophistication, a few investigators sought to assess the elastic modulus of bone as a measure of the state of healing in fractures or the ability of bone to resist fracture. They employed both the theory and practice that had begun to mature a decade earlier for nondestructive testing of structural materials using ultrasound. *In vitro* experiments conducted in a variety of laboratories confirmed that ultrasound yielded quantitative information directly related to the elastic modulus, density, and breaking strength of bone [17, 23–27]. Because of the difficulty of performing accurate and repeatable mechanical testing, versus the better reliability of ultrasound, Ashman [27] ultimately relied on ultrasound velocity to measure the three orthogonal elastic moduli and the three orthogonal shear moduli of *in vitro* cancellous bone samples. Nevertheless, until recently, successful *in vivo* application did not progress beyond a few limited trials in humans which suggested the potential for clinical use [34, 36], as well as use in horses to detect precursors to stress fracture [49–52].

Several factors appear to have impeded progress toward clinical assessment of bone. Early published reports on clinical assessment of bone evidenced little or no discussion of the extraordinarily large anisotropies and heterogeneities of bone. Failure to select the bone site and design the probe positioning to mitigate anisotropy and heterogeneity precluded attaining reproducibility. Failure to design the ultrasound signal generation, detection and processing to account for the complications of wave propagation in bone likewise hindered accurate ultrasound measurement [1, 2].

Not until 1980 did two independent sets of investigators begin to approach the problem of bone measurement site selection and apparatus design in a manner that would ultimately lead to potential clinical application. Pratt et al. [52] at MIT and Poss at Harvard selected the patella—a bone comprised primarily of cancellous material—and developed a hand-held probe and instrumentation for measuring ultrasound velocity [52, 53]. Langton et al. [3] selected another site with substantial cancellous bone, the calcaneous, and developed a water-bath instrument to assess the attenuation of bone. *In vitro* and clinical tests with various versions of these instruments demonstrated that both approaches could yield reproducible measurements. Furthermore, both the velocity [1, 54–56] and the attenuation [4, 57] appeared to be related to bone density as well as indices of the elastic modulus and strength of bone, and both yielded measures of osteoporosis fracture risk [44, 56].

Analysis of Studies Showing a Relationship Between Ultrasound and Bone Quality

To help clarify issues surrounding ultrasound's relationship to indices of bone quality, the topics and studies described below address the central point of this paper, an hypothesis adapted from Heaney [5].

Hypothesis 1

Ultrasound measures clinically relevant properties of bone in addition to and distinct from bone mass.

Consider a question suggested by many of the studies of bone ultrasound. What causes the reports of the correlation between ultrasound and bone mass to vary widely?

Numerous studies have examined the correlation of bone resonance, apparent velocity, and BUA to BMC or BMD. Statistically significant correlation coefficients have ranged from 0.4 or lower, to approximately 0.9 [1, 58, 59]. Glüer et al. [58] showed for BUA and BMD (SPA) measurements of the calcaneous that BMD could only explain 40–50% of the interpatient variation in BUA, and that the BUA precision could not account for the remainder—thereby suggesting that ultrasound also measures properties of bone different from mass density.

Correlations between ultrasound and bone mass do vary with different study populations, even when using equivalent devices and identical measurement sites. For example, a correlation of 0.70 ($P < 0.001$) for apparent velocity at the patella and BMD at the lumbar spine [46] differs from the 0.51 ($P < 0.001$) correlation for the same investigators, bone sites, and equipment, but different populations. Fujii et al. [47] found a correlation of 0.52 between AVU and DXA BMD at the lumbar spine. Intersite differences complicate comparisons even further: Kvasnicka [60], using an identical ultrasound device, found a correlation of 0.38 ($P < 0.0001$) for AVU versus BMD at the distal forearm. Substantial variation in the correlation coefficients were also reported for BUA versus various measures of bone mass. For example, BUA versus distal forearm SPA yielded 0.8 ($P < 0.001$) for Poll et al. [61], but no significance for Resch et al. [45]. Baran et al. [18] found, for BUA versus BMD of the lumbar spine by DPA, a correlation of 0.607 for all subjects, but only 0.479 for the subset of normal (nonosteoporotic) subjects. In a later study [20], the same group reported 0.606 ($P < 0.0001$) between BUA and spine BMD.

Throughout life, as bone matures and then ages, changes in cortical structure, trabecular architecture, mass density, and amount and quality of collagen occur at various times. Although the variability of reported values for the correlation between ultrasound and bone mass measurements is consistent with Hypothesis 1, insufficient data currently exist to determine the specific origins of the reported variability of correlations between ultrasound and bone mass measures. Nevertheless, a second hypothesis given below might explain the variability of correlations between measurements made with identical ultrasound devices and densitometers at the same bone sites.

Hypothesis 2

The correlation between ultrasound and bone mass measurements depends on the sources of bone quality variation between subjects.

Corollary 2a. The correlation between ultrasound and bone mass measurements is variable, and cannot be compared

between studies, without either selecting comparable subjects for both studies or otherwise controlling for the factors affecting bone quality which are unrelated to bone mass.

Corollary 2b. One can obtain correlations between ultrasound and bone mass measurements that approach 1.0 (diminished by the precision of each device [58]) by choosing a population whose subjects' bone qualities differ primarily in bone mass density, and not in properties unrelated to mass.

Corollary 2c. The degree to which nondensity factors affect bone quality can be investigated by controlling for bone mass. For example, if two groups' bone densities are the same, then differences in bone quality must result from factors unrelated to bone density.

Iso-Density Studies: Controlling for Bone Mass

The foregoing hypotheses and corollaries suggest the potential value of controlling for bone mass in clinical studies, as the following two examples illustrate.

Matching Subjects of Equal BMD. Kimmel et al. [62] cite further evidence that ultrasound may yield information about properties of bone that is potentially pertinent to bone quality. From the multicenter osteoporosis study of Heaney et al. [1], pairs of postmenopausal normal and osteoporotic subjects were matched according to equal BMD. Evidence of vertebral deformity confirmed by two independent readers indicated osteoporosis. The analysis was performed twice: first, matching 38 pairs of normal and osteoporotic subjects according to SPA (g/cm) at the distal forearm; second, matching 46 pairs according to DPA BMD at L2–4. The mean ages of the respective normal and osteoporotic groups were not significantly different. By design, the mean BMD values for the normal and osteoporotic groups, in either case (matching by SPA or by DPA), were indistinguishable. Nevertheless, the apparent velocity of ultrasound at the patella distinguished the normal and osteoporotic groups. For matching by SPA, the AVU was 44 m/second or 2.4% lower in osteoporotic than normals ($P < 0.02$); for DPA, 54 m/second or 2.9% lower ($P < 0.005$). The mean AVU for the entire population of 72 osteoporotic subjects was 73 m/second or 3.8% lower than the mean for the 123 normal subjects.

Kimmel et al. [62] concluded: "AVU in our bone mass-paired groups of osteoporotics and normals tended to be less different (−2.4% [SAP] and −2.9% [sBMD]) than in the whole groups (−3.8%). This might indicate that eliminating the influence of bone mass on AVU measurement leaves mainly its component related to trabecular structure." They also warn: "We assume that patellar bone mass is well correlated to mid-radius or spinal BMD. If patellar bone mass does not follow mid-radius or spinal BMD, then our analysis could be flawed." Thus, this study provides further evidence, but not conclusive proof, that ultrasound provides clinically relevant information about bone quality in addition to and distinct from bone mass.

Selection of Populations to Control for BMD. The recent study by Fujii et al. [47] examined the utility of apparent ultrasound velocity at the patella as a measure of both the quantity and quality of bone. DXA BMD at the spine was compared with AVU in 260 Japanese women. The perimenopausal subset was comprised of women in the fifth decade of life, 11 of whom were premenopausal and 28 postmenopausal. The mean ages and mean BMD values for the two groups were not significantly different, but the mean AVU was 68 m/second (3.5%) lower ($P < 0.01$) in the postmenopausal group. This suggests a clinically relevant difference in bone quality unrelated to bone mass between these two subgroups. With the same caveat by Kimmel cited above, these results corroborate Hypothesis 1, and further suggest that ultrasound may have the ability to detect perimenopausal changes in bone quality earlier than bone densitometry.

Ultrasound Detects Osteoporosis and Fracture Risk Comparably to Bone Mass

Cross-sectional studies of postmenopausal women have shown repeatedly that attenuation and apparent velocity of ultrasound, as well as bone resonance, all discriminate between subjects with versus those without evidence of prior osteoporotic fractures—as defined by a history of low trauma fractures of the hip or wrist, or of the spine (confirmed by radiographic evidence). In several studies, ultrasound exhibited sensitivity and specificity comparable to that of bone mass measurements [1, 19, 20, 46, 47]. Furthermore, despite the limited data available, the ability of AVU or BUA to assess risk of future osteoporosis fracture prospectively compared favorably with that of peripheral bone mass measurements (relative risk ratios in the range of 3–5) [44, 56, 63, 64].

The modest correlations of ultrasound to bone mass measurements found in most of these studies appear not to diminish the clinical utility of the ultrasound measurement. This further suggests that the portion of the ultrasound reading that is correlated with factors other than mass density are related to clinically relevant properties of bone quality.

Bone Quality Assessment in a Large, Population-Based Study of Low Trauma Fracture

This cross-sectional study comprised the first large, population-based, age an sex-proportionate stratified random study of the association of low trauma fracture and apparent velocity of ultrasound (AVU) as a measure of bone quality [65]. To date, a total of 390 subjects 50–59 years of age, in a rural setting participated. Of these, 58 experienced low trauma fractures since age 40 (primarily from falling).

Over the entire population, AVU averaged 68 m/second or 3.5% lower in the group with a history of fracture versus those free of fractures ($P < 0.01$). Females with a history of fracture averaged 39 m/second or 2.1% lower than their counterparts ($P < 0.01$). Similarly, males with a history of fracture averaged 55 m/second or 2.8% lower than their counterparts ($P < 0.01$). The average for females without a history of fracture averaged 5.25% lower than males without fractures. Females with fractures similarly averaged 4.5% below males with a history of fracture. Significant differences ($P < 0.05$) were sustained even after correcting for the dependence of AVU on age.

This is the first such study to show (1) a systematic male-female difference in bone quality determined by ultrasound; (2) a demonstrable difference in bone quality—in a truly randomized population unrelated to the study of osteoporosis—between those with a history of low trauma fractures and those without. Stegman et al. [65] concluded that AVU is an appropriate measure of bone quality for population-based studies, and plan to further study the ability to predict future low-trauma fracture prospectively in this population.

Discussion

Much of the interest in ultrasound has derived from its low cost, freedom from ionizing radiation, portability, and ease of use. The promise that ultrasound might also provide new information about bone quality continues to motivate researchers and commercial developers alike. This paper has attempted to show that, although no single study has yielded conclusive proof, an increasing number of studies give mounting evidence that clinical ultrasound devices for bone assessment can provide new and clinically useful information about *bone quality,* which cannot be derived from bone densitometry alone.

This underscores the need for new *in vitro* and clinical studies which not only challenge Hypothesis 1 but also heed the implications of Hypothesis 2 and its corollaries. The studies of Kimmel et al. [62] and Fujii et al. [47] illustrate the power of controlling variables in complex studies by holding constant, parameters such as bone density. Iso-density, iso-velocity and iso-BUA studies are but a few possibilities for this powerful approach.

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DISCUSSION

DR. PIERCE: You said that you had eliminated the effect of bone mineral density when you compared the ultrasound findings in patients who had a history of fracture with those who did not. However, I wonder if you had taken multiple measurements of bone mineral density for each patient and averaged them, whether you might have seen a difference in bone mineral density between the patients who did and did not have a fracture that could have completely accounted for the difference in the ultrasound findings. I am not really sure that you have demonstrated that ultrasound added anything beyond bone mineral density if you used just a single measurement. The other cohort studies did not include a multivariate analysis controlling for bone mineral density.

DR. BRANDENBURGER: In one study we obtained both single and dual photon results, which were two totally independent sets of measures. We saw the same result. I am not sure that gets at your issue.

In the larger Heaney study we did conduct multivariate analyses, where we looked at bone density, ultrasound velocity, patient height, body mass index, and so forth. We were able to show that even if you eliminate, or control for these other factors, the ultrasound velocity readings still were able to distinguish between osteoporotic and normal individuals. The differences were on the order of about five percent.

DR. HEANEY: Let me just add, Dr. Pierce, that the differences in the ultrasound readings are larger than the percentage figures suggest, simply because the baseline in soft tissue is about 1,500 meters per second. So the differences between groups were actually about ⅙ the whole range that was available in that study.

It appears that your 2.5 percent difference was addressing the error of the method of the bone density readings. However, that is not so much of a problem when you are dealing with the much larger actual difference we have with the ultrasound.

DR. SCHNITZLER: Have you or other investigators ever examined the degenerative changes in the patella, where increased sclerosis within the patella mass or the presence of osteophytes around it might alter ultrasound readings?

DR. BRANDENBURGER: No, we certainly have not. The only thing that we did in our studies was to rule out people with rheumatoid arthritis. However, while we did not rule out anyone with osteoarthritis, we have not looked at those variables separately.