QUANTITATIVE ULTRASOUND OF BONE: MYTH AND REALITY

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Abstract

The interaction of ultrasound with bone provides a potentially rich basis for characterising this tissue in terms of density, elastic properties, and micro-architecture. There was rapid growth in the clinical application of the technique from the late 1980s onwards, despite the absence of a comprehensive scientific base to support the claims being made for ultrasound. This translated into problems in later years, with clinical confidence declining due largely to unrealistic expectations and a failure to address openly the limitations of the technology. This paper addresses three areas where misconceptions have arisen in the context of trabecular bone measurement: the relationship of ultrasonic measurements to bone elastic properties, the ability of ultrasound to characterise bone architecture, and the role of the bone marrow. Paradoxically, declining clinical confidence has occurred alongside a resurgence of interest in the physics of ultrasound propagation in bone. Knowledge of the history and problems of the field is an essential prerequisite if emerging fundamental insights are to be translated into improved and accepted clinical techniques.

Introduction

Ultrasonic bone measurement has a peculiar history, and examining this history gives a better understanding of the problems faced today. Three historical phases are outlined below:

Early phase (1940s-mid 1980s)

Ultrasonic measurement of bone is not a new idea. Back in the earliest days of biomedical ultrasound, skull bone was studied for the purposes of developing transcranial diagnostic ultrasound procedures [1]. Work on ultrasound propagation in skull bone continues today, but the context has shifted from diagnostic ultrasound of the brain to therapeutic high intensity focussed ultrasound. The first studies recognising that ultrasonic measurements of bone could be a useful diagnostic tool in their own right date from the 1950s. Measuring the velocity of ultrasonic waves propagating along a long bone from a transmitter to a receiver was shown to yield information on the progress of healing fractures [2]. The ability of ultrasound to give information about bone density in trabecular bone was known in the 1960s [3]. Ultrasound velocity measurements in small cortical bone specimens were developed as an in vitro tool to determine the elastic properties of bone and assess the elastic anisotropy [4].

With hindsight, we can look back over this early period of bone ultrasound work, dating from the 1940s to the mid-1980s, as a time when diverse studies were being performed and new measurement were being tried. However, without the benefit of recognised clinical applications for these emerging measurements there was no force driving the field forward apart from the imagination and curiosity of individual researchers. At times the work was of a very high standard (see, for example, the work of Fry and Barger [5]). Many of the later developments in this field drew on the insights and tacit knowledge arising from these early studies, but failed to recognise and acknowledge this debt, or to build contacts with the early pioneers. Hence when clinical application of ultrasonic bone measurement did take off, it was seen very largely as a new idea, and the opportunity to involve and learn from the pioneers was not fully exploited.

Clinical applications (mid 1980s - mid 1990s)

The transition out of this "early phase" of ultrasound and bone work dates principally from the demonstration, in the mid-1980s, of a method for measuring the heel bone using an ultrasonic through-transmission method, and the determination of broadband ultrasonic attenuation (attenuation slope) as an indicator of bone density [6]. This work coincided with growing realisation of the importance of osteoporosis as a clinical problem and the development of radioisotope, and subsequently x-ray, photon absorptiometry for bone densitometry.

By 1990 several commercial devices for ultrasonic measurement of the heel bone were available and clinical use of the technique was rapidly expanding. The reasons for the enthusiasm were essentially two-fold. Firstly there were the practical advantages of ultrasound as compared to x-ray technology - lower costs, absence of ionising radiation and portability. Secondly there was the possibility that ultrasound could give additional diagnostic information on bone beyond that afforded by conventional x-ray absorptiometry. The hope was that ultrasound would prove to be sensitive to trabecular architecture and bone mechanical properties in addition to bone density.

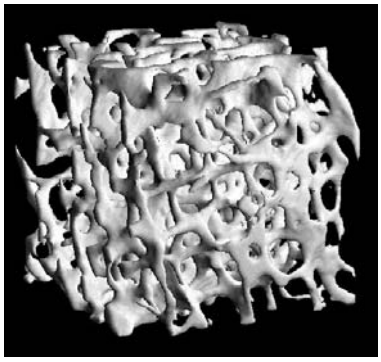

Figure 1: Trabecular bone.
X-ray micro-computed tomography image (courtesy R. Muller, ETH Zurich) showing a 4 x 4 x 4 mm volume of human calcaneal (heel) bone.

There was (and still is) some basis for these hopes, but serious misconceptions arose as to what ultrasound could, and could not, do. In an atmosphere of rapidly growing clinical interest and proliferating commercial devices, words of caution tended to be lost.

It should be noted that this period also saw the introduction of clinical devices for assessing cortical bone, including those based on axial transmission velocity measurements along long bones and transmission measurements across the finger [7]. However, in this paper, the focus is on measurement of heel trabecular bone.

In summary, a period of rapid growth in clinical interest and commercial development occurred in the absence of a firm scientific base, and, predictably, this subsequently led to problems.

Clinical doubts but better science (mid 1990s - today)

The situation we have today is somewhat paradoxical. Clinical confidence in ultrasonic measurements of bone has fallen, but scientific interest in the field is growing. The declining clinical interest stems largely from the unrealistic expectations nurtured during the period of rapid growth in the use of the technique. Ultrasound did not deliver useful information on bone "quality" in addition to "quantity", had longstanding reproducibility problems, and failed to develop standardised measurement definitions and terminology.

On the other hand, since the mid-1990s there has an increasing body of work investigating and quantifying the errors and limitations in the existing ultrasonic bone measurements [7]. Growing interest is being shown amongst the ultrasound physics community; for example as evidenced by the recent inclusion of bone sessions at major ultrasonics and acoustics conferences. Trabecular bone is proving to be one of the most challenging materials known in terms of acoustic characterisation. Trabecular bone is a highly porous anisotropic heterogeneous solid (Fig. 1) saturated with a viscous fatty fluid of variable composition. Several different theoretical models have been proposed and this is a very active area of ongoing work. The challenging nature of the material attracts those used to working with better-behaved porous media, and offers a valuable opportunity to test and extend existing theoretical approaches at the limits of their applicability.

Myth and reality: addressing specific misconceptions

The text above sets the historical context, but the main purpose of this paper is to address three specific areas where misconceptions have arisen concerning the capabilities and limitations of ultrasonic measurements of bone. Note that we are concerned here only with ultrasonic measurements of the trabecular bone of the human heel using the standard transmission approach. This is by far the most widely used measurement approach, though we should not forget the existence of other types of measurement, for instance axial transmission measurement in cortical bone.

We shall first describe the nature of the experimental data that we shall be presenting to illustrate our arguments, and then will go on to deal with the three areas of misunderstanding in turn.

Materials and methods

In this paper, data from a single wide-ranging programme of experimental work using human calcaneal bone are reported. This work was performed with Dr Mary Bouxsein at the Orthopedic Biomechanics Laboratory of Beth Israel Deaconess Medical Center and Harvard Medical School in Boston, USA in 1998-1999. Aspects of this work have been reported elsewhere [8,9] though some results are shown here for the first time.

In summary, ultrasonic measurements were made on 48 trabecular bone cores taken medio-laterally through the calcaneus. The cadaver subjects aged from 50-99 yrs and consisted of 30 females and 18 males. A scanning ultrasonic system with focussed 1 MHz transducers was used, and all ultrasonic measurements were spatially-averaged to reduce random errors. A range of additional physical measurements was performed including x-ray bone densitometry, x-ray micro-computed tomography measurements of bone volume fraction and trabecular architecture, and mechanical testing to determine elastic properties.

Ultrasound and the mechanical properties of bone

Many studies have reported significant correlations between the elastic modulus of trabecular bone, E, and measurements of ultrasonic velocity and attenuation [7]. Note that here we are talking about the modulus of the trabecular framework as a whole, not of trabecular bone tissue at the material level. Figure 2 shows such a relationship in the 48 human trabecular bone specimens.

Correlation does not imply causality. The existence of an association between elastic properties and ultrasonic properties does not mean that a change in elastic properties will cause a change in ultrasonic properties. However, these correlations were often explained by referring to the so-called bar wave equation:

$$c = \sqrt{(E/\rho)}$$

Clearly this equation does imply a causal link between velocity, c, and both E and density, ρ. The crucial point is that this equation is not valid for ultrasonic measurements of fluid-filled trabecular bone at clinically-used frequencies, for at least two reasons. The main reason is that the equation is derived for wave propagation in a homogeneous solid medium, and trabecular bone is not at all homogeneous but on the contrary is a highly porous two phase medium, as we have already seen (Fig. 1). The simple theory of solids cannot be applied in such materials. Potentially valid theoretical approaches are those that account for the presence of the two phases and their interaction, and include mixture law and scattering approaches, Biot's theory, and theories for stratified media.

A second problem in proposing to apply the bar wave equation is that it refers to wave propagation

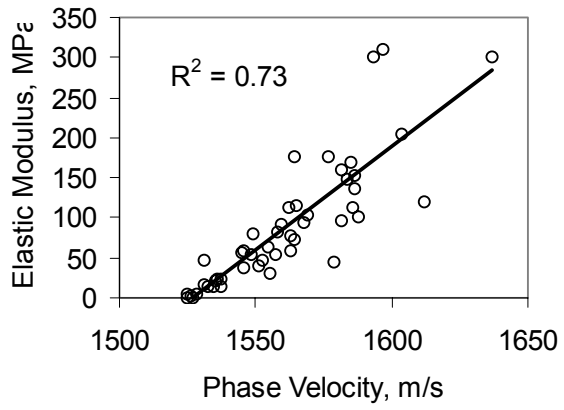

Figure 2. Correlation between elastic (Young's) modulus of the trabecular framework and ultrasonic phase velocity in human trabecular bone

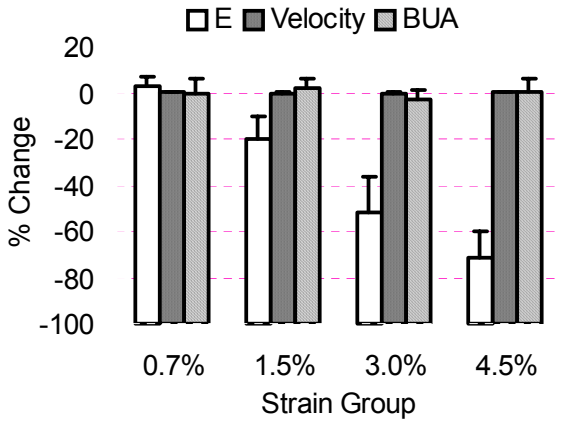

Figure 3. Changes in elastic modulus (E), ultrasound velocity and BUA after mechanical damage.

in a solid specimen whose lateral dimensions are much less than the wavelength. Such a situation is never encountered in clinical measurements of bone.

What is required is a direct experimental test for causal associations between ultrasonic measurements and E in fluid saturated human trabecular bone. To achieve this we measured trabecular bone cores using quantitative ultrasound, and then subjected them to a mechanical loading regime designed to induce limited damage, reducing the elastic modulus but causing negligible changes in specimen dimensions and the trabecular structure [8]. Specimens were randomised into four groups: a control group subjected to a nominally non-destructive 0.7% maximum strain, and three damage groups subjected to maximum strain levels of 1.5, 3.0 and 4.5% respectively. The ultrasonic properties of damaged bone were unchanged despite reductions in E of up to 72% (Fig. 3), confirming that, in the absence of apparent density or architectural changes, ultrasound does not reflect changes in E.

The implications of this finding are profound. Clinically, it means that ultrasound cannot be expected to detect bone fragility in the absence of density or architectural changes. For example, we can imagine situations where bone is subjected to acute overloading resulting in extensive microcracking and reductions in the modulus of the trabecular framework, but the density and architecture could be relatively unchanged. Such bone would be at high risk of subsequent fracture, but our results suggest, this would not be detected by current quantitative ultrasound measurements.

There are also implications in terms of the validity, or otherwise, of certain theoretical models

for wave propagation in bone. Biot's theory has frequently been proposed as a valid for bone, but in Biot's theory the elastic modulus of the solid frame is an explicit determinant of velocity and attenuation. To investigate this further, Biot's theory was used to predict the relationship between frame elastic modulus and velocity in bone. The approach used by Williams [10] was followed, except that the experimentally-derived relationship between frame elastic modulus and bone volume fraction was used in place of a relationship taken from the literature.

Comparing observed to predicted velocities indicates good agreement (Fig. 4) for intact bone, suggesting that the model may be useful. However, as already noted, Biot's theory predicts a causal relationship between modulus of the trabecular framework and velocity, and the predicted effect is shown in Fig. 5. Note that for this figure, the porosity is fixed at 85% and all variables apart from the frame modulus are fixed. Increasing (decreasing) the frame modulus whilst holding all other parameters constant increases (decreases) the velocity of the fast wave.

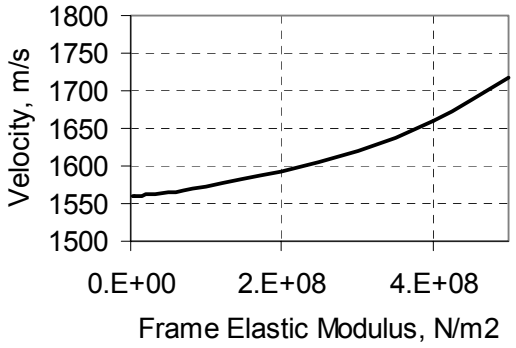

Figure 5. Predicted dependence of ultrasound velocity on frame elastic modulus, all other parameters held constant (porosity =85%).

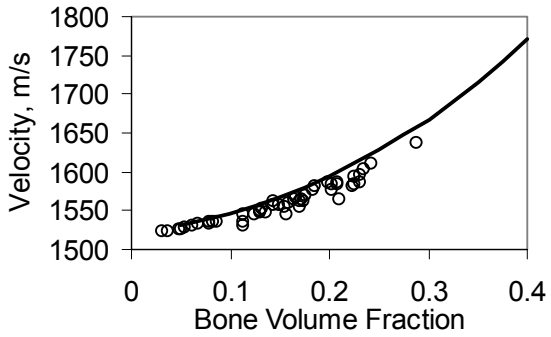

Figure 4. Ultrasonic velocity as a function of bone volume fraction. Experimental data shown as open circles; Biot's theory prediction shown as solid line.

Figure 6 compares the Biot predictions for effects of elastic modulus change to the experimental data from the damage study described above. Biot's theory predicted a velocity decrease of up to 0.4% but experimentally no significant changes in velocity were observed. This suggests that Biot's theory may not be a good model for human calcaneal trabecular bone measured in the medio-lateral orientation. However, the changes predicted by Biot are very small (less than 0.5% decrease in velocity for a modulus decrease of over 70%), and so this comparison does not represent a strong test for the validity of the theory. On the other hand these observations do tell us that if you want to detect changes in the elastic modulus of the trabecular framework in the absence of wider changes, ultrasonic velocity measurements as currently employed are not likely to be of any practical use.

Ultrasound and trabecular architecture

Osteoporosis is defined as a loss of bone and changes in bone architecture leading to increased fragility [7]. Conventional bone densitometry based on x-ray absorptiometry represents a very useful and reliable measurement of bone mass and density, but tells us nothing about trabecular architecture. In vivo x-ray computed tomography with a resolution sufficient to image trabecular architecture is starting to become technically feasible, but the radiation dose is high and it remains a research tool only. If ultrasound were able to provide independent information about both bone density and bone architecture this would be a significant step forward, and a forceful justification for the wider use of ultrasound for bone assessment.

Interestingly, the original work describing in vivo heel measurement with ultrasound was concerned

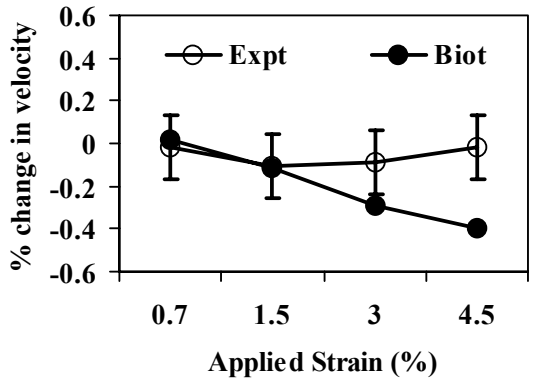

Figure 6. Experimental change in velocity after mechanical damage compared with predicted changes according to Biot's theory.

purely with the possibility of predicting of bone density [6]. The idea that ultrasound might reflect architecture came later. Evidence quickly emerged that ultrasound could, under certain circumstances, reflect architectural factors. For example, the ultrasonic properties of trabecular bone cubes depend on the orientation of the cube [11]. This implies that ultrasound can, in certain circumstances, reflect architecture independently of density, since density obviously cannot vary with orientation.

During the period of rapid expansion in the clinical use of heel ultrasound, the only data on effects of architecture were those from studies in animal bone, or from human bone measured in different directions. No one had investigated the question under conditions directly relevant to the clinical situation, i.e. using human heel bone, and performing ultrasonic measurements in a single direction (the medio-lateral axis). The mistake was to conclude, or imply, that the data available at the time in the early 1990s supported the idea that clinical measurements provided useful information about trabecular architecture independently of density.

When investigators finally addressed this question directly, the hoped for relationships were either absent or extremely weak [12,13]. In retrospect, the reason is now clear: the apparent density and the architecture of human trabecular bone (in the calcaneus at least) are very tightly correlated. If you have denser bone, there are more trabeculae per unit volume, and the trabeculae are thicker, the pores and smaller, and the structure is more plate-like than rod-like. Hence there is no room for architecture to play much of an independent role in determining ultrasonic properties. This argument is illustrated by Figure 7, in which trabecular thickness has been chosen arbitrarily from amongst a range of architectural parameters studied. Ultrasound, density and architecture are all intercorrelated in human heel bone, often strongly so. Density and architectural properties vary in a parallel fashion: denser bone has more trabeculae, those trabeculae are thicker, and the structure is more plate like. The room for architecture to have a detectable influence on ultrasound, independently of density, is very limited.

However, these comments do not represent the whole story. Whilst there may not, on average, be useful independent relationships between ultrasound and architecture, it remains possible that such relationships could exist for special cases such as specific pathological changes in bone. In such cases, the normal close relationship between density and architecture could become uncoupled,

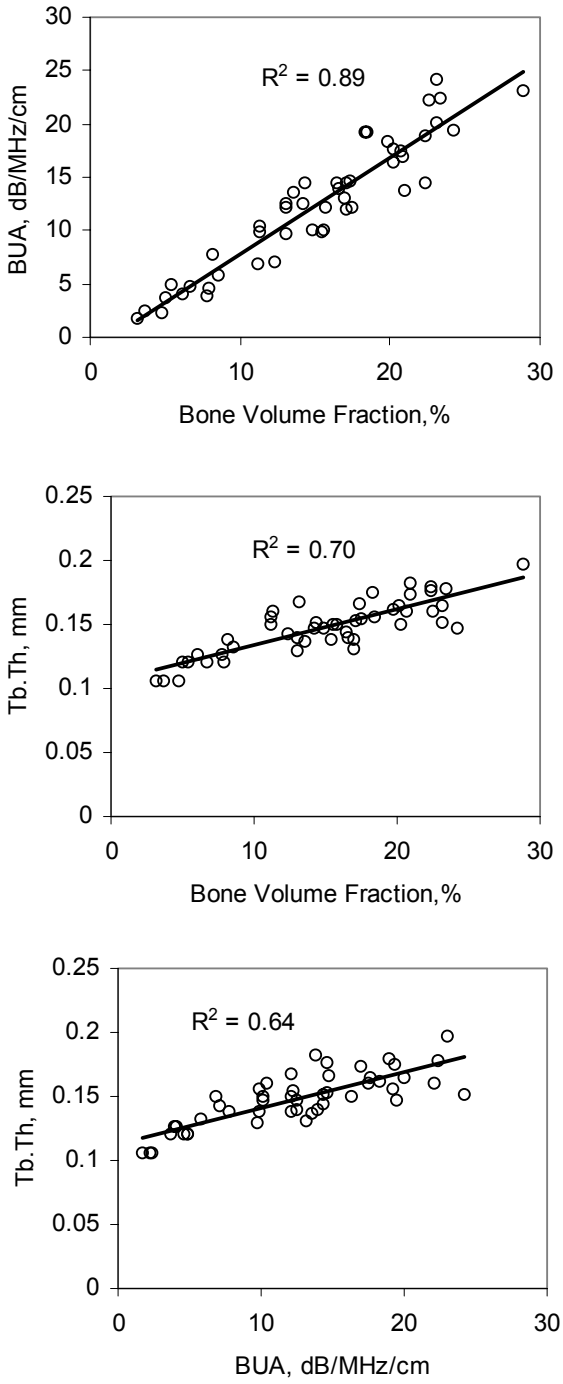

Figure 7. Correlations between ultrasound (BUA), density (bone volume fraction) and trabecular architecture (trabecular thickness, Tb.Th), in human heel bone.

opening up additional room for an independent architectural effect.

Furthermore, the negative findings to date apply to the existing ultrasonic technique based on through-transmission velocity and attenuation measurement. There may be ways of accessing architectural information by modifying existing measurement techniques (e.g. by using different

frequencies) or devising novel techniques (e.g. based on backscatter). If the orientation of the measurement can be varied, then ultrasonic measurements should be sensitive to the structural anisotropy (as in the early cube experiments).

Ultrasound and bone marrow

Trabecular bone from the human calcaneus (heel bone) has a porosity of, typically, 70-95%. So most of what is measured is not bone at all, but rather bone marrow. Bone marrow is a fatty fluid whose composition changes varies with anatomical site, age, race and other factors. There has been suprisingly little work on the influence of the saturating fluid on the ultrasonic properties of trabecular bone. However, in both bovine and human bone, the presence of marrow is associated with decreased velocity and increased attenuation compared to water-saturated bone [9,14].

Our own work [9] indicates that the effects are large. We measured marrow-saturated bone with ultrasound at 35 ^{o}C. The specimens were then defatted by water-jetting and immersion in warm water in an ultrasonic cleaning bath, and were remeasured in the water-saturated state. For example, in human bone from the heel BUA was on average 56% higher in marrow-filled bone compared to water-filled bone (Figure 8).

Now this would not be a major problem clinically provided there was simply a systematic effect due to the presence of marrow. Unfortunately this is not the case. There clearly is a systematic effect, but there is also additional variation consistent with heterogeneity in marrow composition. For example, the effect of marrow on ultrasonic properties differs significantly between males and females, there being larger effects seen in females [9]. One explanation for this could be that females have a higher proportion of fat in the heel bone marrow. The impact of heterogeneity in bone marrow can also been seen in the correlation between ultrasound and bone density: the correlations were significantly weaker when marrow is present (Figure 9). These results imply that there are differences in marrow properties between individuals and confirm that clinical bone measurements will reflect both bone density and marrow properties.

Results such as these make it clear that existing clinical heel measurements cannot be considered as pure "bone" measurements but rather reflect a more complex set of factors associated with the entire volume of tissue traversed by ultrasound. Heel ultrasound, as currently used, is an integral measurement taking in the skin, overlying soft tissue, the cortical surfaces, the bone marrow and the trabecular bone itself. It is possible that part of the (relative) clinical success of heel measurements is due to sensitivity to non-bone factors that are indirectly indicators of skeletal health or more general well-being. For example, low ultrasound velocity could be due to either reduced bone apparent density or to an increased proportion of fat in the marrow. Both are bad news in terms of skeletal health. In the latter case the marrow will contain fewer osteogenic cells and the ability of bone to adapt and maintain itself is likely to be

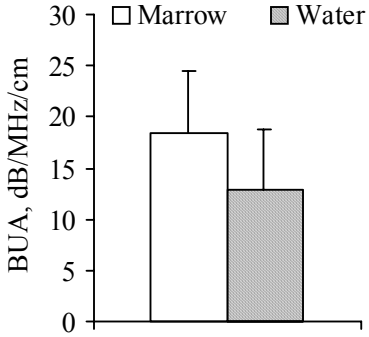

Figure 8. Broadband ultrasonic attenuation in water-saturated and marrow-saturated human trabecular bone.

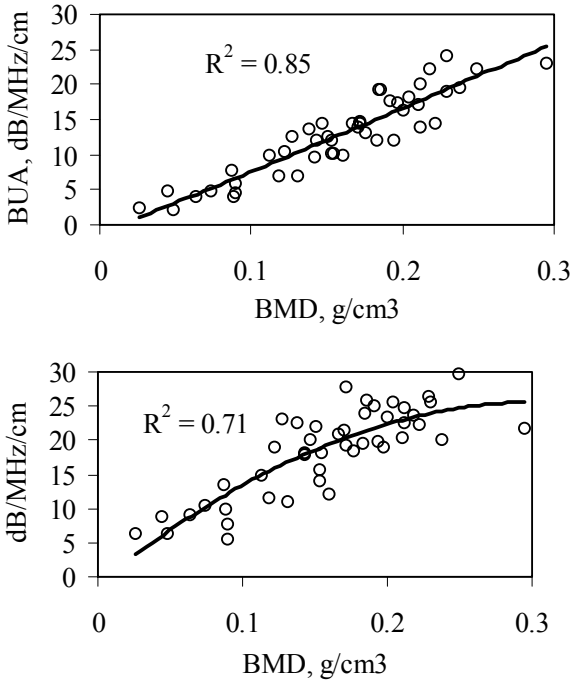

Figure 9. Correlation between BUA and bone mineral density (BMD) in water-saturated (top) and marrow-saturated (bottom) trabecular bone. The correlation is significantly weaker ($p<0.05$) for marrow-saturated bone.

impaired. In this case we can also see how untangling the factors behind the variation in clinical measurements has the potential to lead to new diagnostic avenues, such as the independent characterisation of both bone and marrow.

Conclusions

Paradoxically, clinical interest in ultrasonic bone measurement is declining at a time when physicists are getting increasingly interested in the interaction of ultrasound with bone. The falling clinical interest reflects the failure of quantitative bone ultrasound to live up to unrealistic expectations that arose during a period of rapid uptake of the technology.

In this study we have focussed on some of the areas where misconceptions have arisen regarding heel ultrasound measurements. Although we have not reviewed the evidence here, it is generally accepted that ultrasonic transmission measurements at the heel are clinical predictors of bone density and fracture risk [7]. However, they are not intrinsically related to the elastic properties of the trabecular bone framework, nor do they provide useful independent information on the trabecular architecture. In addition, the properties of the bone marrow have a profound effect on the ultrasonic properties, and bone marrow differs amongst individuals.

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