Background

Osteoporosis is a disease characterised by low bone mass and architectural deterioration of bone tissue. Consequently, there is an increase in bone fragility and susceptibility to fracture. Bone architecture refers to the three dimensional arrangement of trabecular struts. Porosity, connectivity and anisotropy (orientation of the trabecular network) define bone architecture.

In the past 25 years, several non-invasive techniques based on the attenuation of ionising radiation have been developed to quantify bone mineral density in the skeleton. The established techniques vary not only in their source of energy but also in the site and type of bone measured. They represent expensive methods for the determination of bone mineral density, but give limited information on bone structure and strength.

Consequently, there is interest in new methodologies that may have a role in assessing skeletal status. An ideal screening tool should detect skeletal fragility, it should be inexpensive and should be free of ionising radiation. As microfractures and bone architectural changes may also play a role in the process of bone weakening, it is possible that a combination of information on bone structure and bone density will provide a more sensitive tool for fracture prediction than Dual Energy X-ray Absorptiometry.

Ultrasound Densitometry

Langton et al first described the use of ultrasound for the assessment of bone1. This concept is based on the knowledge that the speed of sound and attenuation of a sound wave are affected by the density, compressibility, viscosity, elasticity, and structure of the material it is travelling through. We can use them to investigate the properties of any material, including human bone. Ultrasound can give information about the density and elasticity of bone by measuring the speed of sound through it and about the structure of the bone by measuring the attenuation of the signal. Ultrasound measurements can be made by two methods. The first is pulse-echo (reflection) technique uses a single transducer to transmit and receive the signal. The generated ultrasound pulse travels through the sample and is reflected at an interface to be detected by the same transducer. Secondly, the transmission technique uses one transducer, which acts as a transmitter and the second as a receiver. This technique uses large piezoelectric transducers. For application to bone, the transmission technique is preferred because of the bone's highly attenuating nature.

There is no standard use of terms, or calculation methods for measurement for velocity by ultrasound. This means that speed of sound (SOS), velocity of sound (VOS), apparent speed of sound (ASOS), apparent velocity of ultrasound (AVU) and ultrasound transmission velocity (UTV) all refer to the same generic ultrasound measurement.
Velocity

The principles of ultrasound measurement have been described in section 3. A variety of ultrasound densitometers, using both techniques has been developed over the last three years and allow measurement of a variety of skeletal sites. However, it is difficult to use ultrasound to measure the hip and vertebrae (sites that commonly fracture), because the depth of soft tissue surrounding these bones attenuates too much of the ultrasound signal and a reading cannot be obtained. The most popular measurement site is the calcaneus, and there are several reasons for this:

1 There is very little soft tissue, which makes it easy to measure the bone.

2 It has relatively flat surfaces, which ensures good contact between the heel and the transducers.

3 It is similar in composition to the main fracture sites (approximately 90% trabecular bone).

4 It is easily accessible and requires very little patient preparation.

The basic design of a densitometer for measuring the calcaneus is shown in Figure 1. It consists of a pair of transducers; one to transmit the ultrasound signal and one to receive it, which are positioned either side of the heel. The transducers are either fixed or mobile. Fixed transducers are not in direct contact with the heel and a set heel width is assumed when calculating the speed of sound and broadband ultrasound attenuation (BUA). Mobile transducers are brought into direct contact with the heel and the correct width can be measured.

![Figure 1. Calcaneal fixed single point transmission systems using either water based foot placement or coupling by means of ultrasonic gel](image_url)

A coupling agent is used between the transducers and the skin, as ultrasound does not travel well through air. The coupling agent can be water (“wet” system) or gel (“dry” system). In the wet system the heel is in a water filled bath, whilst in the dry systems gel is used to carry the ultrasound between the transducers and the skin. However GE Lunar has developed a new SmartDry™ system for their Achilles Express and Insight scanners. Here water is self-contained within silicone membranes and ultrasound gel or isopropyl alcohol is used to couple between the skin and the membrane.
Broadband Ultrasound Attenuation (BUA)

For a given material (including bone), the attenuation of the ultrasound wave will always be the same i.e. any material can be given an attenuation value, known as the BUA index. To determine the BUA index of a material, an ultrasound signal covering range of frequencies (broadband) is passed through a known thickness of sample. The amplitude spectrum of the received signal is then compared to the spectrum of a reference material (degassed water). The difference between the two spectra is then plotted against frequency, giving a straightline graph, the slope of which is the BUA index dB/MHz. If this is then divided by the thickness of the measured sample, it gives a true volumetric parameter in dB/MHz/cm. The frequency range of 0.1 to 1 MHz is the most useful for bone characterisation. In clinical practice this has become known as broadband ultrasound attenuation (BUA).

Imaging systems

Focussed transducers allow for images of the site being measured, and allow regions of interest to be verified or even moved. This helps, in particular, with longitudinal measurements as ROI’s can be set to allow the exact site to be re-measured. Some examples of images are shown below:

![Achilles Insight images](image)

![DTU Image](image)

Figure 2. BUA measurement; the left panel shows the comparison of the amplitude spectra for reference and sample material to provide the relationship between attenuation and ultrasound frequency. The right panel shows the slope of the regression over a selected frequency range (usually 0.2 to 0.6 MHz) to give the BUA index.
Table 1. An overview of some of the machines which are currently available. Below are more details, which relate to each machine. Summary of some of the available ultrasound machines in the UK.

<table>
<thead>
<tr>
<th>MACHINE</th>
<th>Parameter Measured</th>
<th>Transducer WIDTH</th>
<th>Transducer SIZE</th>
<th>SITE</th>
<th>Measurement TIME</th>
<th>Temperature RANGE</th>
<th>WEIGHT</th>
<th>Imaging</th>
<th>Wet/Dry</th>
</tr>
</thead>
<tbody>
<tr>
<td>Achilles Express+ (GE Medical Lunar)</td>
<td>Stiffness</td>
<td>25mm</td>
<td>0.5 MHz</td>
<td>Calcaneus</td>
<td>1 min</td>
<td>15-35°C</td>
<td>10kg</td>
<td>No</td>
<td>“SmartDry”</td>
</tr>
<tr>
<td>Achilles Insight (GE Medical Lunar)</td>
<td>Stiffness, BUA &amp; SOS</td>
<td>25mm</td>
<td>0.5 MHz</td>
<td>Calcaneus</td>
<td>&lt; 1 min</td>
<td>15-35°C</td>
<td>10kg</td>
<td>Yes</td>
<td>“SmartDry”</td>
</tr>
<tr>
<td>McCue CUBA Clinical (Norland)</td>
<td>BUA and limb velocity</td>
<td>19mm</td>
<td>Unfocussed</td>
<td>1 MHz</td>
<td>Calcaneus</td>
<td>2 mins</td>
<td>10-40°C</td>
<td>10kg</td>
<td>No</td>
</tr>
<tr>
<td>Sahara (Hologic)</td>
<td>BUA and limb velocity</td>
<td>19mm</td>
<td>Unfocussed</td>
<td>0.5 MHz</td>
<td>Calcaneus</td>
<td>&lt; 1 min</td>
<td>10-40°C</td>
<td>8.2kg</td>
<td>No</td>
</tr>
<tr>
<td>QUS-2 (Quidel Metra)</td>
<td>BUA</td>
<td>32mm</td>
<td>Unfocussed</td>
<td>0.5 MHz</td>
<td>Calcaneus</td>
<td>5 mins</td>
<td>10-55°C</td>
<td>3.2kg</td>
<td>No</td>
</tr>
<tr>
<td>UBIS 5000 (DMS)</td>
<td>BUA, SOS, BUB</td>
<td>29mm</td>
<td>Focussed</td>
<td></td>
<td>Calcaneus</td>
<td>3 min</td>
<td>15-32°C</td>
<td>27 kg</td>
<td>Yes</td>
</tr>
<tr>
<td>DTU-One UltraSure (Osteometer)</td>
<td>BUA and SOS</td>
<td>29 mm</td>
<td>Focussed</td>
<td></td>
<td>Calcaneus</td>
<td>3 min</td>
<td>15-30°C</td>
<td>29 kg</td>
<td>Yes</td>
</tr>
<tr>
<td>DBM Sonic BP (IGEA)</td>
<td>Amplitude dependent SOS &amp; Ultrasound Bone Profiler Index (UBPI)</td>
<td>16 mm</td>
<td>Unfocussed</td>
<td>1.25 MHz</td>
<td>Proximal phalanges</td>
<td>&lt; 3 mins</td>
<td>10-40°C</td>
<td>14kg</td>
<td>No</td>
</tr>
<tr>
<td>Omnisense 7000S/8000S (Sunlight)</td>
<td>SOS</td>
<td>Varies</td>
<td>4-6, 1.2 (0.5-2.1) MHz</td>
<td>Distal radius, Proximal phalanges, Metatarsus V, Mid shaft tibia</td>
<td>&lt; 1 min per site</td>
<td>15-30°C</td>
<td>7kg</td>
<td>No</td>
<td>Dry</td>
</tr>
</tbody>
</table>

Ultrasound Machines Available

Achilles+ (GE Medical Lunar)

The Lunar Achilles+ is a water-based machine\(^3\). A surfactant is added to the water to eliminate the air bubbles which would affect the measurement. The subject's heel is cleaned with an alcohol wipe before measurement. The natural oils, which are present on the skin, affect the transmission of the signal and therefore have to be removed. In addition to SOS and BUA, it also reports another parameter called Stiffness. This is a factor derived from normalised SOS and BUA. This index is claimed to improve precision over velocity and BUA alone, not only normalising for heel width but also for the temperature dependence of the measurements because temperature has opposite effects on BUA and SOS.

The calculation for Stiffness is as follows:

\[
\text{Stiffness} = 0.28 \times \text{SOS} + 0.67 \times \text{BUA} - 420.
\]

The Achilles Express is an externally dry system using Lunar’s SmartDry technology. The membranes are coated with a water soluble gel or isopropyl alcohol before use. An LCD touch screen for the display and controls is connected to the external computer which can store up to 100 measurements before down loading to an external computer. The Achilles Insight is similar to the Achilles Express but has a real-time preview image of the heel and a movable region of interest for optimal positioning.
McCue CUBA Clinical (Norland)

The pads are in direct contact with the skin over the calcaneus\(^4\). A water-based gel is used for coupling the transducer to the patient's heel. This iterative algorithm ensures consistency of coupling and positioning. BUA values are not normalised for heel thickness. Langton et al\(^4\) gives a detailed description of this machine. It has an automated mechanism to ensure constant pressure during the measurement (removing any operator dependence). It also has an enhanced calf support and foot inserts to improve positioning. The new version of the software (after the initial closing of the transducer pads) allows a 30-second settling period before the first measurement. This will reduce the soft tissue effects on the measurement. The measurements are then made without any repositioning of the foot. The unit also has an in-built electronic phantom. The McCue CUBA Clinical is also available in a paediatric version.

Quidel QUS–2 (Biomedx)

The QUS-2 calcaneal ultrasonometer is a self-contained unit that can function without external computer support or an AC power outlet. The transducers are mobile and locate and scan a 1cm\(^2\) region of interest of the calcaneus. The region of interest is supposed to approximate the Vogel spot, which is a site of low bone density (similar to the Ward's triangle area of the hip). A water-based gel is used as a coupling medium. The manufacturer recommends that the gel is applied to the calcaneus four minutes before the measurement is taken (this will increase the total examination time). The results are reported as BUA and UBI (which is the BUA corrected for heel width).

DBM Sonic Bone profiler (IGEA)

This is a self-contained unit which eliminates the need for a separate computer. It incorporates an automated measurement procedure, which reduces the operator effect and simplifies the training procedure. The fingers were chosen as a measurement site because there is cortical and trabecular bone present at the ends of the proximal phalanges in the metaphysis. The mediolateral surfaces of the fingers are approximately parallel and therefore reduce the ultrasound scattering\(^5\). The time of flight of the ultrasound signal is defined as the time from the emitted pulse to received signal that is above a predetermined amplitude value. When a normal bone is tested, the amplitude of the first signal received is above the predetermined threshold, but for osteoporotic bone significant attenuation occurs and the amplitude of the first signal is not enough to trigger the reading. Thus, the measured velocity is amplitude dependent. This enables the differences in SOS measured between normal and osteoporotic bone to be magnified.

The results are expressed as amplitude dependent speed of sound (AD-SoS). A water-based gel is used for coupling. It is important to note that cream on the subject's hands can affect the measurement. The cream acts as a barrier and the ultrasound signal cannot be transmitted effectively. This can result in a low AD-SoS for an otherwise healthy individual.

If a subject cannot remove rings from their fingers then the finger is excluded from the measurement. Under normal circumstances the non-dominant hand would be measured, but it is common to find that some women cannot remove their wedding ring. The dominant hand would then be measured.
Omnisense (Sunlight)

The Sunlight Omnisense uses reflection technology to measure the speed of sound along a fixed distance of bone parallel to its axis, and not across the bone as with other systems. It consists of a desk-top system and small hand held probes of differing sizes to measure the different sites. The probe includes both the transmitters and receivers. SOS only is measured.

UBA575 Walker Sonix (Hologic)

The Walker Sonix UBA575 was the first commercial system for the assessment of bone status. From the initial work of Langton et al. a prototype instrument UBA1001 was developed by Walker Sonix Inc. This system had a variable-frequency tone burst generator. The generator produced a sequence of short bursts of single frequency ultrasound rather than a broadband pulse. The UBA1001 provided only BUA measurements carried out in a room-temperature water bath. This machine is no longer available.

Sahara (Hologic)

This dry system has replaced the UBA 575 Walker Sonix wet system. The Sahara differs from the other dry contact system. The transducers are angled and therefore fit the shape of the heel better. The transducers are motorised and this ensures that the same pressure is applied to each measurement and consequently removes the operator dependence. There is a leg support, which aids in the positioning of the patient. In addition to BUA and SOS the Sahara gives a combined output parameter of the ‘quantitative ultrasound index’ or QUI. The QUI is a combination of the BUA and SOS, but the calculation of QUI differs from that of Lunar Stiffness. The intent of having the QUI parameter is to have a single standard output (rather than two) which the manufacturers claim has the fracture sensitivity of BUA and the high precision of SOS. QUI is calculated using the following equation: \[ \text{QUI} = 0.41 \times \text{SOS} + 0.41 \times \text{BUA-571} \]

UBIS 5000 (DMS)

This device operates in transmission mode and provide BUA images of the heel that are obtained using a pair of broadband focussed transducers immersed in a room temperature water bath. The ultrasound beam (3-5 mm diameter) scans across the heel in 1mm steps to image the entire calcaneus. The advantage of the image is that it allows measurement of artifacts to be identified and avoided. The size, form and location of the region of interest are adjustable by the operator. The image permits the evaluation of standardised regions of interest in all patients as well as the use for larger regions of interest, which improves precision.
The DTU-one operates in the same way as the UBIS machine. BUA and SOS are measured and an image is generated. This allows for regions of interest to be created to ensure consistent measurement sites. The heel is supported in the water bath by a rubber ring in the footwell.

**Approaches to Validation**

There are a number of potential clinical applications for QUS; one of the main ones is the prediction of fracture risk. QUS can predict fracture in an elderly population^{7-9} and has more recently been shown to predict fractures in younger subjects^{10-12}. From this, we can conclude that QUS has the same predictive ability as DXA. QUS could be used for the evaluation and monitoring of osteoporosis. It is essential that for the clinical use of QUS that it should be able to rank individuals within the normal population, detect subtle abnormalities and quantify relatively small changes in individual subjects. Precision error is a major factor in the ability to monitor therapy and with improving precision errors it may be possible to monitor with QUS^{13}.

In order for QUS to be validated, it needs a precise and accurate method for comparison. Dual Energy X-ray Absorptiometry is the method against which QUS can be judged. Direct comparison is difficult. Bone has a mechanically anisotropic structure. In contrast to bone density measurements, which are based on X-ray attenuation, ultrasound parameters reflect the structural anisotropy of bone. Therefore, QUS may have a greater potential to be developed into a method for the comprehensive noninvasive assessment of three dimensional structure and strength. In practical terms, this would be very difficult to do, especially with the current measurement sites. It would require ultrasonic assessment in several directions, at different frequencies, and with a differing beam profile. QUS measurements may complement the bone density measurements rather than replacing them. Site matched BMD and QUS measurements have shown moderate correlation but not strong enough for us to conclude that one method can predict the other^{14}.

**Accuracy**

Ultrasound propagation in bone is complex. Mineral content and other material and structural properties affect ultrasonic attenuation and velocity. Therefore, accuracy has to be expressed in relation to these properties.

There are a number of factors, which affect accuracy and precision. The anatomically incorrect placement of the measurement region is one of these^{15}. As a wider population is studied these factors become even more important.

Diffraction affects both attenuation and velocity measurements and reflects a source of error, which is device specific. Variability of bone width, soft tissue thickness or composition, marrow composition, and temperature represent patient dependent components of accuracy errors^{16}.
Can QUS be Used to Monitor Treatment?
There is limited experience of monitoring skeletal changes solely by means of QUS. The periods to follow individual subjects would most likely exceed those required for bone densitometry. This would probably result in follow up periods of several years. This would not be useful in clinical practice. If QUS measurements are to be of practical use in monitoring response to therapy, it needs to be shown that (1) QUS can reliably detect differences in response between individuals, and (2) that these differences can predict long-term differences in bone mass that are not simply due to measurement error. The ability of QUS to distinguish between subjects in terms of therapeutic response will depend on the magnitude of the response, the heterogeneity of the response between individuals, and the within-subject reproducibility of the QUS measurements.

Quality Assurance
The stability of ultrasound machines has now become more of an issue. Until recently little attention has been paid to how the ultrasound machine is affected when the transducers or the heel bath are changed on a machine. It is important to have the machines serviced regularly and to keep accurate records of any factors, which may affect the stability of the machine. The manufacturers provide their own phantoms for machine calibration and quality assurance. Phantoms for ultrasound machines are still in their developmental stages. Stable phantoms are required so that it is easy to detect if the machine is drifting due to deterioration of a component of the machine, for example the transducers. It is difficult to provide a phantom which is not affected by temperature, or that is made of a material, which itself does not deteriorate. Universal phantoms that can be measured on a number of machines are also currently being developed. It is hoped that with the production of these phantoms we will be able to detect more accurately any changes in the stability of the machine. Until such phantoms are developed, human subjects may be used to measure the stability of a machine. In normal healthy people the measurement values should remain stable. If they are measured on a regular basis then it may be possible to detect changes which are only machine related\textsuperscript{17}.

Conclusions
QUS is rapid, non-ionising and low price. The precision and stability may not be as good as the standard methods e.g. DXA, but the manufacturers are aware of this and are working towards improvement. It does show promise, particularly for fracture prediction in women over 65 years. There are other machines available in addition to the ones mentioned here. More work needs to be done on comparing machines to make a recommendation about which would be the best buy for purchasers.
Ultrasound References