The role of quantitative ultrasound in the assessment of bone: a review

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Received 20 May 1997; accepted 5 August 1997
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Summary

Quantitative ultrasound (QUS) bone measurement is a promising, relatively new technique for the diagnosis of osteoporosis. Unlike to the more established method of bone densitometry [measurement of bone mineral density (BMD) e.g. using dual X-ray absorptiometry (DEXA)], QUS does not use ionizing radiation. It is cheaper, takes up less space and is easier to use than densitometry techniques. The two QUS parameters currently measured are broadband ultrasound attenuation (BUA) and speed of sound (SOS). The reported age-related changes for healthy women range from −0·27% to −1·62% per year for BUA and from −0·06% to −0·19% per year for SOS. Precision ranges from 1·0 to 3·8% (CV) for BUA and from 0·19 to 0·30% (CV) for SOS. The new method of imaging ultrasound has improved the precision of QUS measurements. QUS is significantly correlated with BMD. Studies with the latest equipment have shown *r*-values between 0·6 and 0·9 in site-specific measurements, and QUS is thus believed to reflect mainly BMD. However, other studies indicate that QUS measures something other than the actual mineral content of bone, namely bone quality, e.g. *in vitro* studies have shown that QUS reflects trabecular orientation independently of BMD. In both cross-sectional and prospective studies, QUS seems to be as good a predictor of osteoporotic fractures as BMD. In two large prospective studies, QUS also predicted fracture risk independently of BMD. QUS has just begun to be used systematically for monitoring the response to anti-osteoporotic treatments in prospective trials. In the studies performed, QUS has been found to be useful in the follow-up of patients. QUS is thus a promising new technique for bone assessment.

Keywords: bone mineral density, bone quality, broadband ultrasound attenuation, fractures, osteoporosis, speed of sound, ultrasound.

Introduction

Osteoporosis is a major health problem in terms of both the cost to society and the cost to afflicted individuals. This is especially true of patients with hip fractures, who experience a high rate of mortality and morbidity (Miller, 1978). The incidence of osteoporotic fractures is growing as a result of the rise in life expectancy, and a three fold increase in worldwide fracture incidence is expected over the next 60 years (Melton *et al*., 1992). Identifying individuals at risk is therefore of prime importance as prevention is possible, e.g. using hormone replacement therapy (HRT; Consensus Development Conference, 1993).

Measurement of bone mineral density (BMD) by bone densitometry is currently the most important predictor of osteoporotic fractures (Consensus Development Conference, 1993). BMD can be measured at different skeletal sites by a variety of non-invasive methods. Most commonly used are single-energy X-ray absorptiometry (SEXA; Kelly *et al*., 1994) and dual-energy X-ray absorptiometry (DEXA; Hansen

et al., 1990). However, these techniques use ionizing radiation making quantitative ultrasound (QUS), a technique based on acoustic waves above the audible frequency range, an attractive alternative. Furthermore, ultrasound technology is cheaper, takes up less space and is easier to use than densitometry techniques. DEXA is very accurate for determining bone mineral density and it correlates with bone strength (Bjarnason *et al.*, 1996).

It has been suggested that QUS not only provides information about bone density but also about bone elasticity and bone microarchitecture (Ashman *et al.*, 1984; Kaufman & Einhorn, 1993; Tavakoli & Evans, 1993), which are important factors in determining bone strength (Einhorn, 1992). These factors have collectively been termed 'bone quality'. QUS is measured at the distal radius, the os calcis, the tibia, the phalanges and at the patella (Foldes *et al.*, 1995; Gnudi *et al.*, 1995; Kann *et al.*, 1995; Stegman *et al.*, 1995; Turner *et al.*, 1995). The two QUS parameters measured are speed of sound (SOS) and, at the calcaneus also, broadband ultrasound attenuation (BUA). It has been shown that BUA and SOS are significantly decreased in women with hip fractures (Langton *et al.*, 1984; Baran *et al.*, 1988; Agren *et al.*, 1991) and in women with spinal fractures (Baran *et al.*, 1988; Heany *et al.*, 1989; Resch *et al.*, 1990; Gonelli *et al.*, 1995; Ross *et al.*, 1995). However, the correlation between QUS and BMD at various skeletal sites has been found to vary considerably with *r*-values between 0·29 and 0·88 (Baran *et al.*, 1991; Kroger *et al.*, 1995). These apparently irreconcilable findings could both be true if QUS measures something other than the actual mineral content of bone, namely bone quality.

This review will address the following issues: (1) the theory behind ultrasonic assessment of bone; (2) age-related changes and precision of QUS measurements; (3) correlation of ultrasound with BMD; (4) bone quality or quantity; (5) ultrasound and fractures; and (6) the role of QUS in monitoring the treatment and prevention of osteoporosis. This review is based on articles found through a search of the MedLine system (time period 1 January 1980 to 1 April 1997), a search of the Current Contents system (time period 11 February 1996 to 1 April 1997) and on abstracts from the 17th and 18th Annual Meetings of the American Society for Bone and Mineral Research, September 1995 and 1996, and the 25th European Symposium on Calcified Tissues, April 1997.

Theory behind ultrasonic assessment of bone

Ultrasound consists of acoustic waves above the audible frequency range, i.e. frequencies higher than 20 kHz. These are pressure waves and are thus free of ionizing radiation, in contrast to electromagnetic waves, such as X-rays (Kaufman & Einhorn, 1993). In most medical diagnostic applications (obstetric ultrasound scans, etc.), frequencies above 2 MHz are used to obtain the highest possible image resolution. Such scan are based on a pulse–echo technique, where the same ultrasound transducer is acting both as the transmitter and as the receiver. However, when using ultrasound for the assessment of bone, a transmission technology is usually us. A transducer on one side of the bone is acting as the transmitter and another transducer on the other side is acting as the receiver. Owing to the high attenuation in bone, frequencies in the 200–600 kHz range are typically used. The attenuation of acoustic waves increases with increasing frequency, and transmission of frequencies above 1 MHz will usually result in very weak signals being received with a poor signal-to-noise ratio.

The os calcis is the most widely used bone for ultrasonic measurement for several reasons: (1) It has two nearly plane-parallel sides; (2) it is surrounded only by a thin layer of soft tissue; (3) it consists mainly of trabecular bone; and (4) it is also a weight-bearing bone.

Water or gel is used to obtain the necessary acoustical contact between the transducers and the tissue. Here, we will focus on the heel as the measurement site and water as the coupling media. The two basic parameters measured by QUS are BUA and SOS, given in units of (dB MHz^{-1}) and (m s^{-1}) respectively. BUA is derived from the attenuation of several frequencies, while SOS is calculated from the transit time of (in principle) one frequency. Calculation of BUA is by far the most complex compared with SOS. Figure 1 shows a schematic drawing of the measurement set-up: the transmitting transducer, a posterior view of the os calcis with surrounding soft tissue, the receiving transducer and the water bath. A series of sine waves (a burst) is generated electronically and converted to an acoustic signal by the

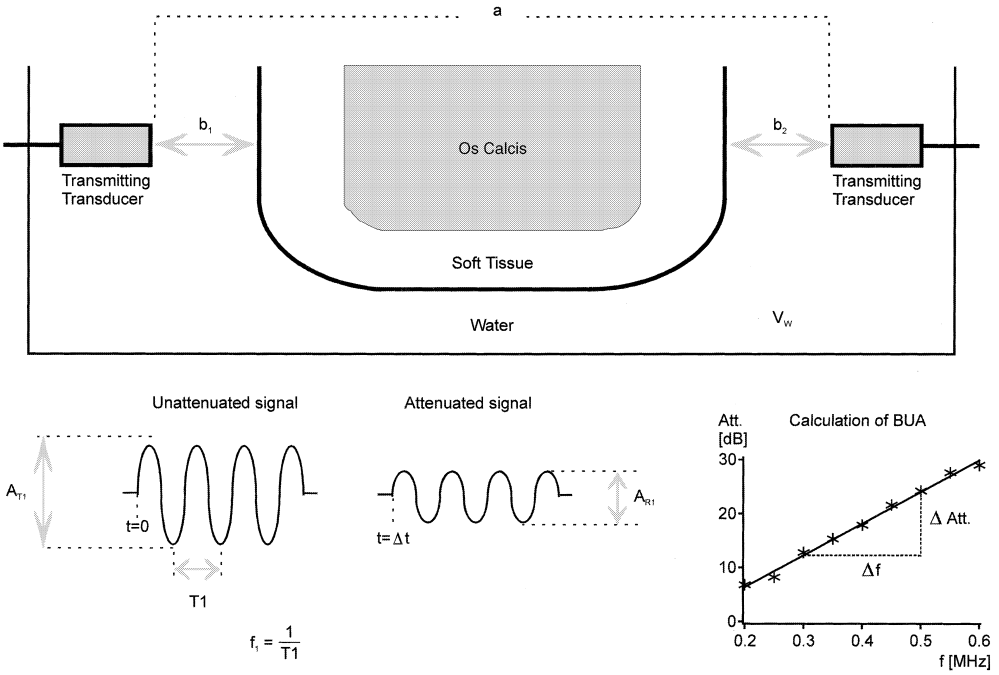

Figure 1 Schematic drawing of ultrasonic measurement. This figure shows schematically the transmitting transducer, a posterior view of the os calcis with surrounding soft tissue, the receiving transducer and the water bath. A series of sine waves (a burst) is generated electronically and converted to an acoustic signal by the transmitting transducer. The peak–peak amplitude of the unattenuated signal, A_{T1}, is recorded during a reference measurement with direct contact through water from transmitter to receiver, i.e. without a heel in the ultrasound path. With the heel submerged into the water, the signal is attenuated and the received amplitude is called A_{R1}. BUA is calculated as BUA = Δ Att/Δf (Att = attenuation in dB; f = frequency in MHz).

transmitting transducer. The peak–peak amplitude of the unattenuated signal, A_{T1}, is recorded during a reference measurement with direct contact through water from transmitter to receiver, i.e. without a heel in the ultrasound path. With the heel submerged into the water, the signal is attenuated and the received amplitude is called A_{R1}. The attenuation (Att) expressed in decibel (dB) is calculated as

$$\mathrm{Att}_1 = 20 \log \frac{A_{T1}}{A_{R1}}$$

The frequency is now increased during repeated measurements resulting in a corresponding increase in the calculated attenuation. When a sufficient number of measurement points (frequency, attenuation) are obtained, they can be plotted in a graph as shown in Fig. 1. BUA is calculated as the slope of the line resulting from a simple linear regression:

$$\mathrm{BUA} = \frac{\Delta \mathrm{Att}\ (\mathrm{dB})}{\Delta f\ (\mathrm{MHz})}$$

Another method for measuring BUA is the use of a broadband pulse comprising all the frequencies of a given frequency band. Analysing the attenuated pulse using the fast Fourier transform (FFT) algorithm and a linear regression provides the same information. Some of the disadvantages of this technique are the large computer capacity required to perform a FFT analysis and the relatively large sensitivity to noise.

BUA is sometimes normalized for the width of the os calcis to reflect a truer expression of the condition of the bone (yielding a unit of dB $\mathrm{MHz}^{-1}\mathrm{cm}^{-1}$). Measurement of the width of the os calcis can be done by measuring the thickness of the soft tissue around the os calcis. Such measurements are associated with error sources, such as estimating the speed of sound in the soft tissue. The diagnostic value of a normalized BUA does not seem to be increased compared with a non-normalized BUA (Wu *et al.*, 1995).

SOS is derived from the time delay, Δt, of a burst, as shown in Fig. 1. The burst is transmitted at the time $t = 0$, and it is detected by the receiver at the time

$t = \Delta t$. SOS is calculated as $SOS = a/\Delta t$, where a is the distance between the transducers. This is the most basic way of calculating SOS. Water, soft tissue and bone are included in this measurement. To exclude the influence of water and soft tissue the distance from transducer to the soft tissue and the thickness of the soft tissue have to be known. This can theoretically be done by using the pulse–echo technique. In order to obtain a precise distance measurement, however, much higher frequencies than 600 kHz must be used. One of the most important potential error sources with this technique is, again, the uncertainty of the speed of sound in the soft tissue. A more common technique is, therefore, to exclude solely the influence of water. SOS can then be calculated as:

$$SOS = \frac{a - b_1 - b_2}{\Delta t - \frac{b_1 + b_2}{V_w}}$$

Here, $a - b_1 - b_2$ is the heel width and V_w is the speed of sound in water as shown in Fig. 1. As the frequency dependency of SOS is insignificant, the highest frequency is usually used. The arrival times of the higher frequencies are easier to detect, as the slope of the sine waves is higher. When measured at the patella, the speed of sound is often referred to as the apparent velocity of ultrasound (AVU) for two reasons: (1) it represents the combined effects of the thin soft tissue layer as well as the spatially varying velocity across the anteriomedial aspect of the patella; (2) the arrival time estimator uses the first zero-crossing of the received signal rather than the actual wave front (Brandenburger *et al.*, 1990).

BUA and SOS can be combined mathematically to a third parameter, the stiffness index (SI). SI is calculated automatically by the software of some commercially available ultrasound measurement systems, e.g. the Achilles system (Lunar, Madison, WI, USA) where it is defined as: $SI = 0{\cdot}67 \times BUA + 0{\cdot}28 \times SOS - 420$. The use of other parameters, such as the absolute amplitude, are currently under investigation.

Imaging ultrasound is an interesting new technique for bone assessment (Laugier *et al.*, 1994). Very fast digital signal processors now make it possible to calculate averaged amplitude, BUA and SOS images, and such scanners are now commercially available. A great advantage of imaging is the possibility of defining a region of interest (ROI). The calcaneus has an area in the tuber in which the attenuation is particularly low, and this area is most often used as the ROI (Jørgensen & Hassager, 1997; Roux *et al.*, 1996). This ensures that, in different patients and in repeated measurements of the same patient, the same area of the bone is assessed, independently of the overall heel size. Imaging techniques have improved the precision of QUS (Jørgensen & Hassager, 1997), thereby increasing the feasibility of follow-up studies.

Age-related changes and precision of QUS measurements

Table 1 shows the age-related changes of BUA and SOS at the os calcis in healthy females. For BUA, the reported annual change ranges from −0·27% to −1·62% and, for SOS, from −0·06% to −0·19%. As can be seen, most authors find an accelerated loss after the menopause. The studies in Table 1 are all cross-sectional and therefore potentially biased by confounding factors. However, in a 2-year prospective study of 113 post-menopausal women, Schott *et al.* (1995a) reported an annual decrease (SD) of −1% (4·3%) for BUA and a decrease of −0·8% (0·6%) for SOS. Aside from the influence of age on QUS measurements, it has also been shown that anthropometric parameters, such as height, weight and heel width, are significant predictors of QUS values (Hans *et al.*, 1995a).

Table 2 shows the short-term *in vivo* precision (expressed as coefficient of variation, CV%) of BUA and SOS measured at the os calcis. Only studies with four or more measurements per individual (with repositioning of the foot between each measurement) and five or more individuals have been included. In these studies, the CV% of BUA varies from 1·0% to 3·8% and the CV% of SOS from 0·19% to 0·3%. The CV% of SOS is thus roughly 10 times smaller than that of BUA. Higher CV% (up to 10% for BUA) have been reported, especially in older studies using experimental equipment (Zagzebski *et al.*, 1991). The precision in relation to the annual changes can be calculated as the ratio between the CV% and the percentage change per decade. This ratio should be as small as possible. The figure is about 1·5%/7% = 0·2 for BUA, 0·2%/1·2% = 0·17 for SOS of the calcaneus and 1·5%/15% = 0·1 for BMD measured at the femoral neck (Pouilles *et al.*, 1993; Engelke *et al.*, 1995; Graafmans *et al.*, 1996; Takeda *et al.*, 1996)

Table 1 Age-related changes in BUA and SOS at the os calcis.

Author	% Change per year	r	n (age range)	Effect of menopause
BUA				
Krieg *et al.* (1996)	−0·44	−0·29	176 (64–98)	NA
Takeda *et al.* (1996)	−0·32	−0·52	473 (20–69)	Yes
Moris *et al.* (1995)	−0·27	−0·60	118 (20–80)	No
van Daele *et al.* (1994)	−0·40	−0·28	777 (55–85)	NA
Salamone *et al.* (1994)	−0·51	−0·14	259 (45–75)	NA
Schott *et al.* (1993)	−0·56	−0·56	512 (20–90)	No loss between 20–50 years
Palacios *et al.* (1993)	−1·62	?	111 (30–70)	No loss between 30–50 years
Herd *et al.* (1993)	−1·22	−0·31	170 (40–70)	ysm < 5: ra = 2%, ysm > 5: ra = 0.5%
Roux *et al.* (1993)	−0·67	−0·37	190 (45–80)	Yes
Herd *et al.* (1992)	−1·01	−0·31	200 (40–70)	ysm < 5: ra = 2.5%, ysm > 5: ra = 0.5%
SOS				
Krieg *et al.* (1996)	−0·05	−0·21	176 (64–98)	NA
Takeda *et al.* (1996)	−0·11	−0·67	473 (20–69)	NA
Moris *et al.* (1995)	−0·09	−0·63	118 (20–80)	No
van Daele *et al.* (1994)	−0·10	−0·39	777 (55–85)	NA
Schott *et al.* (1993)	−0·07	−0·66	512 (20–90)	No
Herd *et al.* (1993)	−0·19	−0·33	170 (40–70)	ysm < 5: ra = 0.3%, ysm > 5: ra = 0.03%

The % change per age range was either stated specifically in each article or else it was calculated from the regression equation. Only studies with more than 100 subjects (all female) are shown. Some studies included only post-menopausal women, and the possible effect of the menopause in those studies is therefore not applicable (NA). When stated, the annual rate of loss (ra) in relation to years since menopause (ysm) is shown. The % change per year is calculated for all the studies as $R_A = \sqrt[T]{1 + R_T} - 1$, where R_T is the rate of change over T years and R_A is the annual rate of change.

Table 2 Short-term precision of BUA and SOS at the os calcis.

Author	Apparatus	Number of measurements	Coefficient of variation (CV%)
BUA			
Baran *et al.* (1991)	UBA 575	6 × 22	2·9 ± 0·6
Damilakis *et al.* (1992)	UBA 575	5 × 5	3·8 ± 1·4
Roux *et al.* (1993)	UBA 575	5 × 30	2·9 ± 1·7
Lees & Stevenson (1993)	Achilles	5 × 5	1·4 ± 0·5
Kawana *et al.* (1994)	Achilles	10 × 5	1·0
Moris *et al.* (1995)	Achilles	4 × 10	1·6
Graafmans *et al.* (1996)	CUBA	5 × 20	3·4
SOS			
Lees & Stevenson (1993)	Achilles	5 × 5	0·19 ± 0·08
Kawan *et al.* (1994)	Achilles	10 × 5	0·3
Moris *et al.* (1995)	Achilles	4 × 10	0·2
Graafmans *et al.* (1996)	CUBA	5 × 20	1·4

The number of measurements is shown as measurements per individual × the number of individuals. The coefficient of variation is represented as mean ± SD (if reported). Only studies with four or more measurements (with repositioning of the foot between each measurement) and five or more individuals are shown in this table. The Achilles system is from Lunar Corp, USA; the UBA 575 is from Walker Sonix, USA; and the CUBA system is from McCue Ultrasonics, UK.

when using CVs for the modern systems and annual changes for post-menopausal women.

Many potential error sources may have an influence on the precision of QUS measurements. The side difference between the right and left calcaneus is about 7·5% (Dretakis *et al.*, 1994a), making it important always to measure the same site, especially in longitudinal studies. Inter- and intraobserver variations has been shown to be of some importance. In a multicentre (five centres) study by Hans *et al.* (1994), the CV% for calcaneal BUA was found to be 1·1%, 2·2%, 2·5%, 2·3% and 1·2% for the five centres respectively. For calcaneal SOS, the CV% was 0·20%, 0·22%, 0·30%, 0·26% and 0·17% respectively. In another study assessing tibial ultrasound velocity, the short-term interobserver CV% was slightly higher than the intraobserver CV%, 0·50% and 0·35% respectively (Orgee *et al.*, 1996).

In a study by Evans *et al.* (1995), the influence of several factors on the precision of calcaneal BUA was investigated. A 5° rotation about the long axis of the leg gave rise to a BUA error of 9·2%, a 2 mm heel–toe translation resulted in an error of 9·2%, a 1 cm translation across the water tank resulted in an error of 2% and equipment stability resulted in an error of 2·6%. The other factors (immersion time, water depth, water temperature, volume of detergent, rotation about the long axis of the foot and translation dorsal–plantar) all gave rise to errors smaller than 2%. The position of the foot in the water bath is thus of crucial importance to the reproducibility of QUS measurements. Studies using imaging ultrasound have shown a tremendous heterogeneity of the acoustic properties of the calcaneus, providing a good explanation for Evan's findings (Laugier *et al.*, 1994, 1996).

Considering the relatively small annual changes in QUS measurements (Table 1), it is essential that everything is done to optimize precision. A step in this direction has been taken with the introduction of ultrasound parametric imaging that is now used in commercially available scanners. These techniques make it possible to locate a region of interest (ROI). Two studies have investigated the reproducibility of QUS with the use of an ROI. Roux *et al.* (1996) found an average short-term coefficient of variation of 1·4% in a study with ROIs of different sizes. They also compared imaging QUS with BMD and found an *r*-value of 0·88 for site-specific BUA and BMD measured at the calcaneus. Another study by Jørgensen and Hassager (1997) compared BUA measurements using an ROI with measurements using a fixed position relative to the water bath, as is done in regular scanners. They found the precision at the ROI to be significantly better than at the fixed position (CVs were 1·20% and 3·87% respectively). The use of an ROI thus seems to improve the precision of QUS measurements. However, no studies have yet directly compared these new scanners with the non-imaging systems. As can be seen in Table 2, the non-imaging systems have shown CVs down to 1·0%. More studies comparing the new scanners with the old ones are needed in order to determine exactly how much is gained in precision with ultrasound imaging.

Correlation of ultrasound with BMD *in vivo*

Many authors have investigated the correlation of QUS parameters with densitometry measurements *in vivo* (Table 3). The *r*-values of these investigations are of course dependent on the age range and sex of the participants. In that respect, they are somewhat heterogeneous. We have, however, tried to summarize these investigations in Table 3, giving the range of the coefficients and a weighted mean value.

As might be expected, the correlations are best when QUS is measured at the same site as BMD, e.g. $r = 0{\cdot}66$ for BUA v. BMD at the os calcis as opposed to $r = 0{\cdot}47$ for BUA at the os calcis v. BMD at the lumbar spine (Table 3). This is also the case in individual studies on the same populations (Salamone *et al.*, 1994; Brooke Wavell *et al.*, 1995; Crepin *et al.*, 1994; Ross *et al.*, 1995). The values for the correlations shown in Table 3 are based on both new and old studies. There is a tendency towards higher correlations in the more recent studies, e.g. site-specific measurements of BUA and BMD correlate with *r*-values around 0·8 in recent studies (Graafmans *et al.*, 1996; Roux *et al.*, 1996).

These simple linear regressions assume a direct relationship between QUS and BMD. But even though the correlations are significant, the *r*-values are too small for precise prediction of BMD by QUS measurements. This may be because of either imprecision or the fact that QUS and BMD measure different things. As will be seen in the next section, this is a matter of much dispute at the time.

Table 3 Correlation of QUS parameters with BMD at different sites.

	BMD femoral neck	BMD spine	BMD calcaneus	BMD distal radius
BUA calcaneus	0·47 (0·30–0·87)	0·47 (0·32–0·83)	0·66 (0·53–0·74)	0·37 (0·29–0·42)
	8042 (25)	9212 (28)	1221 (7)	1226 (4)
SOS calcaneus	0·52 (0·35–0·73)	0·53 (0·33–0·77)	0·47 (0·44–0·50)	0·33
	4981 (14)	5545 (15)	148 (2)	170 (1)
SI calcaneus	0·61 (0·45–0·77)	0·62 (0·43–0·80)		0·37
	3193 (9)	4027 (12)		170 (1)
SOS patella		0·36 (0·34–0·41)		0·36 (0·32–0·43)
		346 (3)		1428 (2)
SOS tibia	0·40 (0·31–0·47)			0·63
	527 (2)			307 (1)
SOS distal radius				0·68
				313 (1)

The first line of an entry shows the weighted mean with the range shown in brackets. This value was calculated as follows: $r_{MEAN} = (N_{i1}\ r_{i1} + N_{i2} r_{i2} + ...)/(N_{i1} + N_{i2} + ...)$. The total number of individuals is shown for each weighted r_{MEAN}. The second line gives the total number of subjects with the number of studies in brackets. This table is based on the following references: (Baran *et al.*, 1991; Brooke Wavell *et al.*, 1995; Crepin *et al.*, 1995; Cunningham *et al.*, 1996; Faulkner *et al.*, 1994; Foldes *et al.*, 1995; Fujii *et al.*, 1994; Funke *et al.*, 1993; Glüer *et al.*, 1992; Gnudi *et al.*, 1995; Gonelli *et al.*, 1995; Graafmans *et al.*, 1996; Herd *et al.*, 1994; Kolthoff *et al.*,1995; Kroger *et al.*, 1995; Lees and Stevenson, 1993; Massie *et al.*, 1993; McCloskey *et al.*, 1990; Moris *et al.*,1995; Palacios *et al.*, 1993; Poet *et al.*, 1994; Rosenthall *et al.*, 1995, 1996; Ross *et al.*, 1995; Roux *et al.*, 1993, 1996; Salamone *et al.*, 1994; Schott *et al.*, 1993, 1995b; Stegman *et al.*, 1995; Takeda *et al.*, 1996; Truscott *et al.*, 1992; Turner *et al.*, 1995; van Daele *et al.*, 1994; Wapniarz *et al.*, 1993; Waud *et al.*, 1992; Yamasaki *et al.*, 1994; Young *et al.*, 1993).

Bone quantity or quality?

A large number of studies have been carried out in order to address the central question, i.e. to determine what exactly is measured by QUS. The regression between BMD and BUA is different when measured in trabecular than in cortical bone (Palmer & Langton, 1987). As BUA is only measured at the calcaneus, which consists mainly of trabecular bone, only measurements on trabecular bone are considered here. When measured *in vitro*, site-specific measurements of QUS and BMD on trabecular bone show high correlation coefficients with *r*-values above 0·8 (Laugier *et al.*, 1997). One might then jump to the conclusion that QUS reflects only BMD. But could it tell us something more about the properties of the bone? The properties of bone that determine its ultimate strength include various other properties, such as the material properties of the bone matrix and the microarchitecture of trabecular bone (Einhorn, 1992). In this article, 'bone quality' will refer to these properties altogether. BMD reflects bone quality (Glüer *et al.*, 1994; Alves *et al.*, 1996) as well, so a strong correlation with BMD does not necessarily mean that QUS does not reflect bone quality.

Studies with orthogonal measurements on cubes of bovine trabecular bone have shown that BUA and UVB (ultrasound velocity through bone) depend on trabecular orientation (Glüer *et al.*, 1993; Njeh *et al.*, 1996; Duquette *et al.*, 1997). Glüer *et al.* (1993) found that BUA was about 50% larger when measured along the axis of the compressive trabeculae compared with the two perpendicular axes, even though BMD was the same in all directions. In another study, Glüer *et al.* (1994) studied the dependency of BUA, UVB and UAB (ultrasound attenuation in bone, a measure of the mean attenuation of ultrasound in bone) upon bone structure assessed by microcomputerized tomography. They found all three QUS parameters to be significantly associated with bone structure independently of BMD. UVB was largely influenced by trabecular separation, UAB by connectivity (degree of connection of trabecular fibres) and BUA by a combination of both. However, a study by Hans *et al.* (1995b) on the association of QUS with bone microarchitecture assessed by histomorphometry found all QUS parameters to be associated with microarchitecture, but none of the relations remained significant after adjusting for BMD.

Another way of assessing the properties of bone is to test mechanical properties, such as the elasticity

and compressive strength. In such a study, Langton *et al.* (1996) found that BUA normalized for the width of the calcaneus was a good predictor of both strength and elasticity of defatted cylinders of calcaneal bone, but normalized BUA in combination with apparent density (dry weight/volume) was not a better predictor of these parameters than apparent density alone. Also, apparent density was a better predictor of these properties ($r^2 = 0{\cdot}885$ for elasticity and 0·876 for strength) than BUA (r^2-values 0·722 and 0·693 respectively). However, in a study comparing the load-bearing capacities of whole calcanei that were compressed in the load-bearing direction [where Langton *et al.* (1996) compressed in the mediolateral direction], BUA was a better predictor than BMD of all compressive properties (failure load, stiffness and energy absorption), but a combination of the two did not provide any additional information (Han *et al.*, 1997). So, apparently, the methods compare differently when the bone is stressed in different directions and, in that respect, one might also expect different results when the stress is placed on a different bone, i.e. the femur or lower vertebrae, where most osteoporotic fractures occur. One study compared BUA and BMD measurements with the failure loads of 16 matched sets of cadaveric femurs and feet (Bouxsein *et al.*, 1995). It showed a significant relationship between BUA of the calcaneus and failure load, but not after controlling for femoral BMD. In a preliminary report from another study, the relationship between calcaneal ultrasound and vertebral strength on 62 cadavers was investigated (Cheng *et al.*, 1997). A weak correlation was found between QUS and vertebral strength ($r = 0{\cdot}33$ and 0·37 for UVB and BUA respectively).

On the basis of the present evidence, it is clear that QUS parameters correlate strongly with BMD and are correlated to trabecular orientation. It is not clear, however, whether QUS provides any additional information in the prediction of bone quality. Although some of the studies mentioned in this section show a relation between QUS and bone quality, there has been criticism that the variance in, for example, trabecular orientation might not be large enough to make a difference when measuring along a single axis and at the same site (Laugier *et al.*, 1997). Most of the *in vitro* studies mentioned above included 20 samples or less, which might not be enough to show a significant difference in multivariate analysis when the various parameters are so closely related. Thus, we may conclude that, if QUS provides information about bone quality, it is probably qualities that are partly reflected by BMD. But the final proof is still missing and will probably demand considerably larger investigations than the ones performed until now.

Ultrasound and fractures

Cross-sectional studies

A large number of cross-sectional studies have been made in order to determine if ultrasound parameters are able to discriminate patients with osteoporotic fractures from non-fracture patients and how they compare with BMD measured by DEXA.

Figure 2 shows the ability of QUS values at the os calcis to distinguish fracture patients (hip, wrist and spine) from control subjects. The BUA values are significantly lower in the fracture groups than in the control groups except in one study by Stewart *et al.* (1995) involving 245 women. In this study, receiver operating characteristics (ROC) analysis for predicting vertebral deformation/fracture yielded an area under the curve (AUC) value for BUA at the os calcis of only 0·56 against an AUC of 0·72 for BMD at the lumbar spine. In the same study, 249 men were also examined, but neither the BMD measurements nor BUA were able to discriminate between the fracture and control groups for males.

Several of the studies in Fig. 2 have compared QUS with densitometry. All but Stewart *et al.* have found BUA measured at the os calcis to be as good as BMD measured at the hip or lumbar spine at discriminating fracture patients from control subjects, in studies of hip, vertebral or wrist fractures, whereas SOS in some cases showed a slightly lower association (Resch *et al.*, 1990; Stewart *et al.*, 1994; Funke *et al.*, 1995; Gonelli *et al.*, 1995; Kroger *et al.*, 1995; Ross *et al.*, 1995; Schott *et al.*, 1995b; Turner *et al.*, 1995; Glüer *et al.*, 1996). Bauer *et al.* (1995) found an independent relation between BUA at the os calcis and vertebral fracture and between BMD and vertebral fracture by looking at the risk of vertebral fracture across tertiles of both BUA and BMD of the spine.

In an epidemiological study of 1428 patients (The Saunders County Bone Quality Study), AVU at the

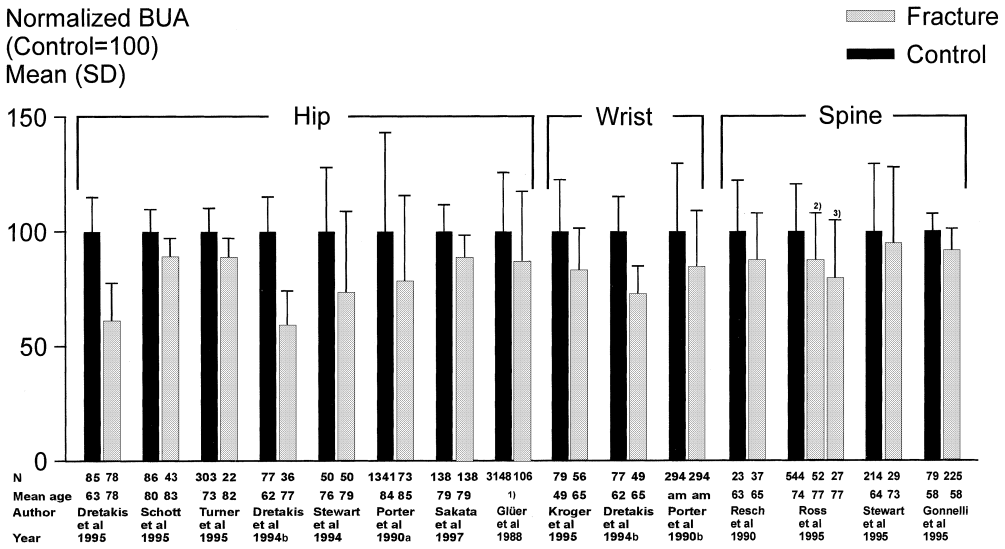

Figure 2 Fracture discrimination by QUS values at the os calcis. The bars show means ± 1 SD. BUA values are normalized; controls = 100. *P*-values for differences between the fracture group and control subjects range from 0·0001 to 0·04, except in one study by Stewart *et al.* (1995) where no significant difference was found between the spine fracture group and the control group. The area under the curve (AUC) by ROC analysis was found to be 0·79 for BUA, 0·85 for SOS, 0·83 for SI against 0·78 for BMD at the femoral neck by Turner *et al.* (1995). Stewart *et al.* (1994) found the AUC for BUA to be 0·76 vs. 0·62 for BMD at the femoral neck. AM, Age-matched. [1]Mean age not reported. [2]One spinal deformation. [3]Two or more spinal deformations.

patella was found to be better than single-photon absorptiometry at the forearm in estimating the odds of vertebral fractures (Stegman *et al.*, 1995, 1996; Travers-Gustafson *et al.*, 1995). Measurements of SOS at the tibia have also been able to recognize patients with fractures (Funck *et al.*, 1996).

Thus, in cross-sectional studies, QUS values are consistently found by almost all authors to be lower in subjects with osteoporotic fractures. Furthermore, almost all studies comparing QUS and densitometry find QUS to be as good as densitometry for fracture discrimination.

Prospective studies

Compared with the large number of cross-sectional population studies, relatively few prospective studies have been performed. In a study by Porter *et al.* (1990a) of 1414 women aged over 69 years in residential care over a 2-year period, measurement of BUA at the os calcis was combined with a clinical assessment of cognizance and mobility. The women in the highest risk group (low BUA index and cognizance testing) had a hip fracture incidence of 12·8% compared with only 1·5% in the low-risk group (relative risk = 8·4).

Figure 3 shows the relative risks of fracture at different skeletal sites comparing QUS with densitometry in two large prospective studies, the 'Study of Osteoporotic Fractures' (SOF; Bauer *et al.*, 1997) and the EPIDOS study (Hans *et al.*, 1996). These studies examine very large numbers of patients, $n = 5662$ (EPIDOS) and $n = 6189$ (SOF). As can be seen from Fig. 3, they support the finding that QUS is able to predict fractures and, in both studies, QUS was also found to be independent of BMD. After controlling for BMD, both BUA and SOS remained predictive of hip fracture. Other, smaller, prospective studies have also shown that QUS can predict fractures (Heaney *et al.*, 1995; van Daele *et al.*, 1995).

In conclusion, people with low ultrasound parameters have a higher risk of low-trauma fractures than others. There is some evidence supporting the theory that ultrasound measurements are not just reflecting BMD values but do provide additional information. However, this requires further investigation.

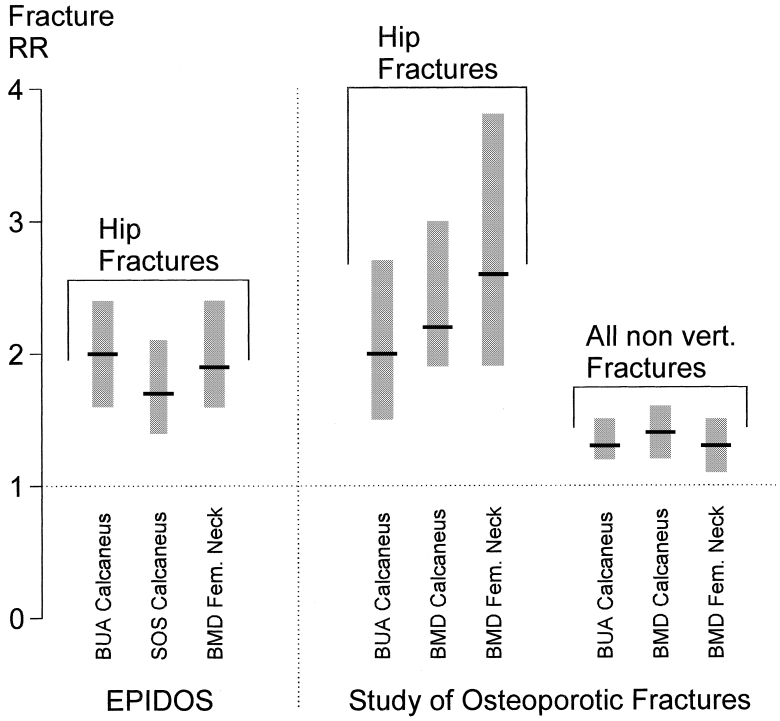

Figure 3 Prospective fracture risk studies. Relative fracture risk (RR) with 95% confidence interval is shown, all studies using −1 SD as cut-off point. (vert, vertebral).

The role of QUS in monitoring the treatment and prevention of osteoporosis

QUS has just begun to be used systematically for monitoring the response to anti-osteoporotic treatments in double-blind prospective clinical trials. Preliminary results from a study of 48 patients randomly allocated to intermittent slow-release sodium fluoride (SR-NaF) and 51 patients allocated to placebo, followed for almost 4 years, showed an increase in the ultrasound velocity of cancellous bone in the SR-NaF-treated group (Pak *et al.*, 1995). No increase was seen in the placebo group.

In another prospective study of 112 osteoporotic women, Gonnelli *et al.* (1996) treated 78 patients with salmon calcitonin nasal spray and calcium and 34 patients only with calcium. After 2 years of follow-up, SOS for the salmon calcitonin group had increased by 0·20%, BUA by 0·88%, SI by 2·12% and BMD by 1·99%. In the calcium-treated group, all parameters had decreased. The differences between the study groups were significant for BMD, SOS and SI, but not for BUA.

A study of 25 women assigned to a brisk walking programme and 15 control subjects showed significant differences between the groups in the changes in BUA and BMD of the calcaneus after 1 year of follow-up (Jones *et al.*, 1991).

In a cross-sectional study, Naessén *et al.* (1995) investigated 35 long-term users (more than 5 years, mean duration 16·2 years) of subdermal oestradiol implants and 35 non-users. In 28 age-matched pairs (mean age 67 years), BUA, SOS and SI was determined at the os calcis. For the implant users, SOS was found to be 1% higher than for the non-users ($P = 0{\cdot}04$), BUA to be 6% higher ($P = 0{\cdot}04$) and SI to be 12% higher ($P = 0{\cdot}03$). In comparison, BMD at the lumbar spine measured by DEXA was 23% higher for the implant users ($P = 0{\cdot}01$).

Thus, QUS seems to have some value in monitoring the effects of treatment of osteoporosis. However, more prospective studies are needed to confirm the usefulness of QUS indicated by these studies.

Conclusion

QUS is a potentially valuable addition to the diagnostic tools for osteoporosis. It is cheaper, does not involve ionizing radiation and is easier to use. Precision has

been a problem with QUS measurements, especially BUA. The reported annual changes in BUA range from 0·3% to 1·6% (Table 1), and high precision is therefore very important. The new generation of scanners with imaging abilities could bring the solution to this problem. They have been shown to improve the precision of QUS (Jørgensen & Hassager, 1997), but more experience with these scanners is needed to determine exactly how precise they are.

In recent studies, site-specific measurements of BUA and BMD have shown high correlations with *r*-values around 0·8. Thus, QUS probably mainly reflects BMD, but many investigations indicate that QUS measures something other than bone density alone. QUS is influenced by trabecular orientation and may thus represent 'bone quality' (Glüer *et al.*, 1993; Stewart *et al.*, 1994; Hans *et al.*, 1995b; Langton *et al.*, 1996; Njeh *et al.*, 1996; Duquette *et al.*, 1997), but the definite proof hereof is not yet available. Furthermore it is not known whether the variation in bone structure and trabecular orientation is great enough to make a difference in single-direction measurements of the calcaneus (Laugier *et al.*, 1997). It is still not clear either exactly which parameter(s) measured by QUS reflect 'bone quality' best. More basic *in vitro* research is clearly needed to identify these parameters.

QUS separates fracture from non-fracture patients as well as BMD in cross-sectional studies (Resch *et al.*, 1990; Stewart *et al.*, 1994; Gonelli *et al.*, 1995; Kroger *et al.*, 1995; Ross *et al.*, 1995; Schott *et al.*, 1995b; Turner *et al.*, 1995; Glüer *et al.*, 1996). Calcaneus BUA also predicts future hip fractures as well as BMD and may even provide additional information on fracture risk. However, more prospective studies are needed to determine whether QUS provides additional information to BMD on fracture risk.

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