Eur Radiol (2009) 19: 1837–1848
DOI 10.1007/s00330-009-1354-1

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Quantitative ultrasound in the assessment of skeletal status

Received: 4 August 2008
Revised: 27 November 2008
Accepted: 2 December 2008
Published online: 4 March 2009

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Abstract Quantitative ultrasound (QUS) is a non-invasive technique for the investigation of bone tissue in several pathologies and clinical conditions, especially in the field of osteoporosis. The versatility of the technique, its low cost and lack of ionising radiation have led to the diffusion of this method worldwide. Several studies have been conducted in the last years to investigate the potential of QUS in multiple areas with promising results; the technique has been applied in the prediction of osteoporotic fractures, in monitoring therapies, in the investigation of secondary osteoporosis, in paediatrics, neonatology and genetics. Our review article gives an overview of the most relevant developments in the field of quantitative ultrasound, both in clinical and in experimental settings.

Keywords Quantitative ultrasound (QUS) · Speed of sound (SoS) · Broadband ultrasound attenuation (BUA) · Amplitude-dependent speed of sound (AD-SoS) · Stiffness · Quantitative ultrasound index (QUI) · Bone quality · Osteoporosis

Introduction

Bones are organs composed of hard and fairly rigid tissues, which absorb energy during loading and can deform without cracking [1].

Their primary function is to resist mechanical forces applied to them by muscle contraction and gravity. To carry out this function, each bone has a species-specific size, shape, and internal structure, the outcome of both evolutionary adaptation in the population and physiologic adaptation in the individual during growth.

Since it is widely recognised that increased susceptibility to fracture is the most important clinical manifestation of many metabolic bone disorders, medicine has focussed attention not only on the haematopoiesis and homeostasis of bone, but also on the mechanical properties of the bone as a whole organ.

Bone is hard, rigid and dense because the matrix is impregnated with an apatite-like mineral; since the latter has accumulated at the expense of water, the volume of the matrix does not change. The density, which is mass per unit volume, of unmineralised bone matrix is about 1.10 g/cm^3; this increases to about 2.35 g/cm^3 when all free matrix water has been replaced by mineral. Tissue density changes little with age and may even increase, old bone having more mineral per unit volume than young bone.

In contrast, the apparent bone mineral density (BMD), which is the density of a whole bone as an organ (mass divided by external volume), falls progressively with age because the external volume does not change or even increases slightly (periosteal expansion with advancing age), and the mineral mass declines as bone is lost [2]. In particular, the loss of bone has different patterns in relation to the type of bone considered, i.e., cortical, trabecular and integral bone in different proportions in long bone diaphyses, metaphyses and epiphyses.

These differences are crucial in considering the characteristics of bone that can be quantified using quantitative ultrasound (QUS). In fact, this technique has been proposed as a measurement that reflects the quality aspects of bone, such as microstructure and geometry, independent of bone mass [3].

In recent years QUS has been widely applied to the investigation of a large number of diseases associated with bone loss and increased fracture risk. Initially these studies provided relevant information, which helped researchers to better understand the mechanism of interaction of ultrasound with various alterations of bone tissue observed in different diseases. Since it is safe and does not require ionising radiation, QUS has been extensively applied in paediatrics [4] and in adults [5], and its wide use has helped clinicians to assess bone health in children and monitor their skeletal growth and development [6]. Recently, QUS has been successfully applied to neonates and premature infants, to study bone maturation and to monitor the bone response to physical stimuli or pharmacological intervention [7].

Cortical bone, trabecular bone

Most mechanical load bearing in the skeleton is carried out by cortical bone, which bears the immediate burden of all skeletal muscle contraction, as all muscles are attached, directly or indirectly, to the periosteum. Even at sites with the highest proportion of trabecular bone, such as the long bone metaphyses and vertebral bodies, fractures begin in cortical bone [8]. The relative loss of bone with age is greater for trabecular bone than for cortical bone, because of its higher surface-to-volume ratio; for this reason trabecular bone tissue is very often investigated to detect conditions of early demineralisation. On the other hand, the absolute amount of bone lost is greater in cortical bone. Furthermore, thinning of vertebral cortices with age contributes substantially to loss of compressive strength of the vertebral bodies, already compromised by trabecular bone loss, and much of the strength of the spinal column as a functional unit is provided by the vertebral arches and the spinous processes, which consist primarily of cortical bone [9].

The structure of cortical bone can be described by two features: thickness, which varies substantially from <1 mm to >10 mm at different skeletal sites, and porosity, which is usually in the range of 2–8% [2]. Both of these characteristics are closely related to bone mechanical properties and competence. Cortical bone predominates in the peripheral skeleton, where the bones usually measured by QUS are located: phalanges, radius, tibia. In the calcaneus the predominance is of trabecular bone (95%), and this peculiarity is of great interest because it is almost the unique peripheral measurable site constituted by trabecular bone.

Quantitative ultrasound methodology

Ultrasound propagation through a material, and particularly in bone, can be characterised by the velocity of transmission and the amplitude of the ultrasound signal [11]. It has been shown that ultrasound velocity reflects the material properties of bone, such as elastic modulus and compressive strength, and that it is influenced by its density, architecture and elasticity [12, 13]. The attenuation of an ultrasound wave through a medium occurs by a reduction in its amplitude and results in a loss of acoustic energy. Thus, two main variables can be measured by QUS devices, derived from the velocity or attenuation of the ultrasound waves through the bone tissue. The QUS variables reflecting ultrasound velocity inside the bone, expressed as m/s, are known as speed of sound (SoS), which is a pure parameter of velocity, independent of ultrasound wave attenuation [11, 12], and amplitude-dependent speed of sound (AD-SoS) that is partly amplitude-dependent [13]. SoS is a variable usually measured by QUS methods applied to the calcaneus, radius and tibia, whereas AD-SoS is measured by the phalangeal QUS device.

The majority of QUS devices are applied to only one skeletal site, such as the proximal phalanges of the hand, the calcaneus and the tibia, but a multisite QUS device is also available, able to measure (by using different probes) one or more skeletal sites, such as the tibia, radius and third phalanx of the hand.

QUS devices differ from one another by their technical characteristics, including frequency of emitted ultrasound waves, pathways of ultrasound transmission inside the bone, skeletal site and region of interest (ROI) measured, bone components examined and QUS variables assessed to estimate bone mineral status and their precision. QUS devices generate pulsed acoustic waves with a range of centre frequency between 500 kHz and 1.25 MHz according to the manufacturer, which is considerably lower than the frequencies commonly used in imaging ultrasonography [11]. Figure 1 shows the main QUS methods and the skeletal sites usually assessed in clinical practice.

The technology of phalangeal and calcaneal QUS devices is based on the principle of the transverse ultrasound transmission (ultrasound transmitters and receivers are placed on opposite sides of the bone being examined with a variable distance between them depending on the

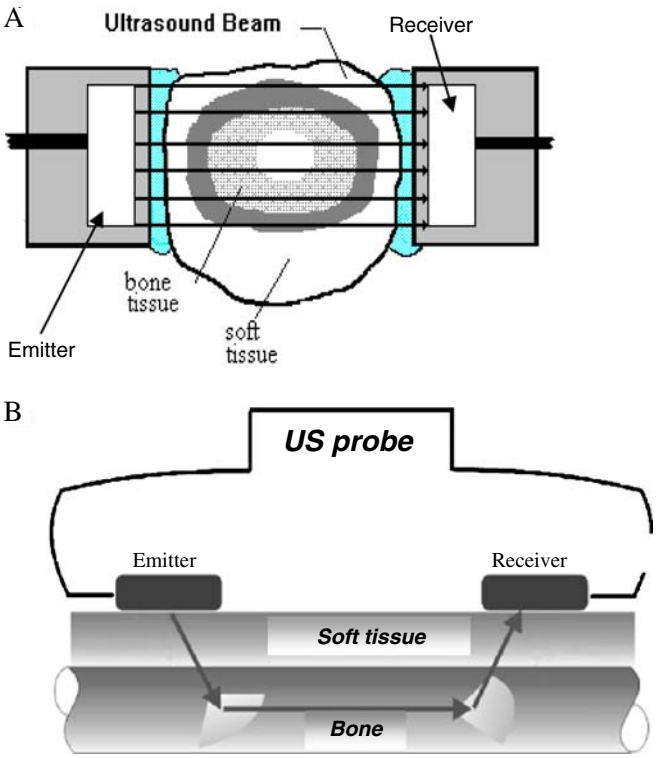

Fig. 1 Theory of ultrasound wave propagation. **a**: Transversal ultrasound transmission, **b**: axial ultrasound transmission

thickness of the bone and the soft tissue), the ultrasound beam being depicted in Fig. 2. Multisite QUS devices equipped with the probe for the mid-tibia and distal third of radius are based on the axial transmission along the cortical bone [reflective; the probe contains a set of two transmitters and two receivers positioned on one side of the bone, at a fixed distance, such that speed of sound (SoS) along the length of the bone is measured by using the "critical angle" concept]; the velocity of an ultrasound wave travelling through a few centimetres of bone and parallel to its axis within the outer 2–6 mm is measured [10]. Short-term precision of QUS variables is similar for SoS, AD-SoS and broadband ultrasound attenuation (BUA) [11], even if the calculated coefficient of variation is not standardised, and is similar to that reported for DXA [12]. Foot positioning is the principal source of measurement imprecision in BUA, caused by regional variation in trabecular bone structure, and this may be a limiting factor in longitudinal measurements.

Ultrasound attenuation through bone is commonly evaluated by broadband ultrasound attenuation (BUA), which is a measure of the frequency dependence of the attenuation of the signal, and is expressed as dB/MHz [11].

Some calcaneus QUS devices provide additional ultrasound variables derived from the mathematical combination of both SoS and BUA, defined as the stiffness index $[(0.67 \times BUA) + (0.28 \times SoS) - 420]$ and quantitative ultrasound index $[0.41 \times (BUA + SoS) - 571]$, expressed as percentages. These parameters have been introduced in order to improve the standardised coefficient of variation of velocity or BUA alone and to compensate for temperature variation [11].

Phalangeal QUS devices, by analysing the changes in the ultrasound graphic trace occurring during propagation through the finger (proximal phalangeal bone), can provide information on the amplitude and the number of peaks of the ultrasound wave that may be useful in certain clinical contexts [14].

Previous studies

Epidemiologic studies

A recent large-cohort epidemiologic study, the "Epidemiological Study On the Prevalence of Osteoporosis" (ESOPO), has been published by Adami et al. [15], examining the association between known risk factors for osteoporosis and QUS measurement at the calcaneus in an Italian population of women and men of 40–80 years of age. To date, this is the only study involving both males and females and including detailed patient history, clinical and lifestyle information associated with risk factors for osteoporosis.

The study demonstrated that the main clinical determinants of QUS measurement are age and weight. In addition, a significant effect of hormone replacement therapy was observed in women. After correction for these factors, recalled body weight at 25 years of age, present and past cigarettes smoked per day, and dairy calcium intake significantly affected the QUS measurement, in addition to prior ovariectomy, history of more than 2 months confined to

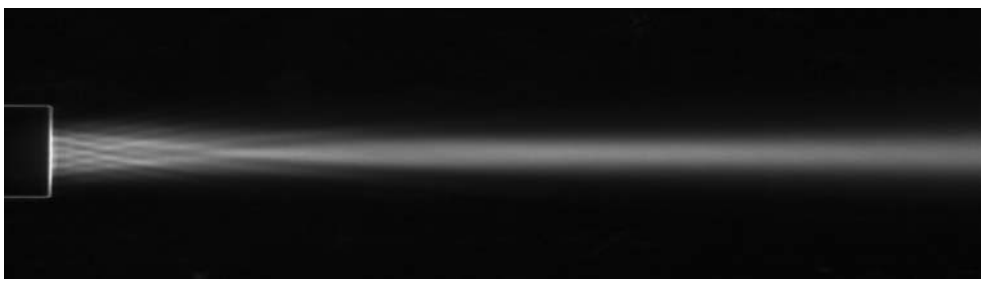

Fig. 2 Picture of the ultrasound wave emitted by a piezoelectric probes at 1.25 MHz

bed, outdoor physical activity, chronic use of any drug and previous glucocorticoid use. Similar results were obtained in men, allowing the authors to conclude that most clinical risk factors for osteoporosis observed in women are equally applicable to men.

Primary osteoporosis

In recent years, three prospective studies have been carried out to assess fracture risk by QUS at the calcaneus [16–18] showing a significant association between heel QUS and fracture prediction. The most recent study, the EPIC-Norfolk prospective population study [19], conducted on a British male and female population, has definitely proved the effectiveness of QUS at the calcaneus in predicting fracture risk. The study involved 14,824 subjects in an age range of 42 to 82 years, with a mean follow-up of 1.9 (0.7) years. The results of the three studies are all reported in Table 1.

The European cross-sectional multicentre study (PhOS) [14], performed on over 10,000 women, provided important confirmation and clinical validation of the QUS method at the phalanx. It demonstrated the high precision (coefficient of variation CV below 1% in both the short and long term) of QUS and the ability to detect osteoporotic subjects with osteoporotic fractures. Another cross-sectional study performed by Guglielmi et al. [20, 21] comparing QUS at the phalanges and X-ray methods (DXA and QCT) found no significant differences between the two techniques using ROC analysis (Table 2), even if the number of cases was limited.

Similar results have also been observed by other authors using QUS at the phalanx and the calcaneus. Hartl et al. [22], in the Basel Osteoporosis Study (BOS) for detecting spinal fractures, have shown that the performance of QUS at the calcaneus and phalanx is comparable with the results obtained with hip DXA (Table 2).

A retrospective and cross-sectional study conducted on an elderly population by Krieg et al. revealed that both QUS methods, at the phalanges and at calcaneus, showed encouraging results in discriminating fracture subjects, though QUS at the calcaneus proved to be more effective in the elderly population [23] (Table 2).

Regarding this aspect, a small but interesting Italian study has outlined how QUS at the phalanx is more sensitive in discriminating subjects with spinal fracture immediately post-menopause, prior to age 70 years, whereas QUS at the calcaneus is more sensitive in later age (over 70 years) [24] (Table 2).

The study by Krieg was then continued prospectively, and the ability of QUS at the calcaneus to predict hip fracture in the Swiss population was confirmed [18]. However, the study had some shortcomings in quality control of the devices and thus did not enable collection of a sufficient number of valid measurements for QUS at the phalanx for a reliable evaluation of the effectiveness of the method in predicting hip fracture in the elderly population [25, 26].

Lastly, the "Osteoporosis and Ultrasound" study (OPUS) has shown that the QUS method at the phalanx and calcaneus is effective in discriminating subjects with spinal fracture in a population recruited in France, the UK and Germany [27] (Table 2).

The International Society for Clinical Densitometry has recently published a position paper [28] on the management of osteoporosis with QUS, where it has been established that heel QUS measures are related to global fracture risk with similar relative risk as other central bone density ROIs for postmenopausal women and for men. Overall some, but not all, heel QUS devices are effective for assessing fracture risk in some, but not all, populations, the evidence being strongest for Caucasian females over 55 years old [29]; this is probably due to the fact that this population is the one more extensively investigated. The highest level of evidence of heel QUS in osteoporotic fracture prediction is outlined, even if it is clearly claimed that not all heel QUS devices perform in the same way in the clinical routine. The importance of accurate quality control programs is reported, in order to obtain the best performances in osteoporosis management.

Table 1 Results of the four main prospective studies on fracture prediction

Study	Parameter	OR	CI 95%
SOF [17]	BUA	2.0	1.5–2.7
	BMD neck	2.6	1.9–3.8
EPIDOS [16]	BUA	2.0	1.6–2.4
	SOS	1.7	1.4–2.1
	BMD neck	1.9	1.6–2.4
EPIC NORFOLK [19]	BUA	4.44	2.24–8.89
SEMOF [18]	BUA	2.4	1.8–3.1
	SOS	2.3	1.7–3.1
	Stiffness	2.6	1.9–3.4

SOS=Speed of sound, BUA=broadband ultrasound attenuation, BMD=bone mineral density, OR=odds ratio, CI 95%=confidence interval and 95% probability

Secondary osteoporosis

The studies of QUS applied in causes of secondary osteoporosis provide a new perspective, as it has definitely introduced the concept of analysis of the ultrasound signal once the latter has crossed the bone tissue. This approach has proved to be fundamental in the study and characterisation of metabolic bone pathologies such as: osteoporosis

Table 2 Area under the ROC curves for discrimination between osteoporotic fractured patients and non-fractured subjects

	BOS [22]	OPUS [27]	SEMOF [23]	PHOS [14]	Guglielmi et al. [20]	Camozzi et al. [24]	
Fractures	Vertebral	Vertebral	Hip	Vertebral	Vertebral	Vertebral	
N	486	1,265	7,562	1,549	140	43	84
Age range	55–65	55–79	70–80	50–80	20–75	60–69	70–79
Parameter	AUC	AUC	AUC	AUC	AUC	AUC	AUC
DXA lumbar spine	0.702*	0.67*	-	0.721*	0.75*	0.71*	0.62
DXA neck	0.660*	0.66*	-	-	-	-	-
DBM Sonic AD-SoS	0.729*	0.65*	0.59*	0.721*	0.70*	0.86*	0.46
DBM Sonic UBPI	0.711*	-	-	0.742*	0.74*	0.75*	0.51
Achilles BUA	0.760*	0.65*	0.74*	-	-	-	-
Achilles SOS	0.746*	0.67*	0.75*	-	-	-	-
Achilles STIFFNESS	0.769*	0.66*	0.77*	-	-	-	-
Sahara BUA	0.787*	-	0.71*	-	-	0.55	0.70*
Sahara SOS	0.761*	-	0.73*	-	-	0.60	0.71*
Sahara QUI	0.778*	-	0.73*	-	-	0.54	0.72*
DTU-1 BUA	-	0.65*	-	-	-	-	-
DTU-1 SOS	-	0.66*	-	-	-	-	-
UBIS 5000 BUA	-	0.65*	-	-	-	-	-
UBIS 5000 SOS	-	0.67*	-	-	-	-	-
QUS-2 BUA	-	0.65*	-	-	-	-	-

*$p<0.05$
AD-SoS=amplitude-dependent speed of sound, UBPI=Ultrasound Bone Profile Index, SOS=speed of sound, BUA=broadband ultrasound attenuation

induced by glucocorticoids [30], rheumatoid arthritis [31, 32], osteomalacia [33], thalassemia [34], osteogenesis imperfecta [35], hyperparathyroidism [36], psoriatic arthritis [37], epilepsy [38] and cystic fibrosis [39]. This has yielded very promising results for the use of QUS.

QUS has already been in use in nephrology for some years. Several studies have employed the method in populations of uremic patients on chronic dialysis [40–49]. Regardless of the site measured (phalanx, tibia, calcaneus), QUS parameters in uremic patients have always been found to be lower than in healthy controls [40–48, 50] (Table 3). The phalanges of the hand, in particular, appear to be the site of choice for measuring bone tissue in such patients because of the greater involvement of cortical bone related to secondary hyperparathyroidism. In the Italian study performed by Montagnani et al. [40], the authors were able to differentiate the group of subjects with high bone turnover from those with low turnover, and thus showed how the AD-SoS and Ultrasound Bone Profile Score (UBPS) measured by QUS at the phalanges were significantly reduced in the high turnover group—unlike the SOS and BUA measured by QUS at the calcaneus. Whereas significant (negative) correlations with dialytic age (years of haemodialysis) were found for the phalanges and tibia, calcaneus measurements did not demonstrate significant correlations with years of haemodialysis [52, 1].

In a recent article by Guglielmi et al. in which osteoporotic and uremic patients with similar bone mineral density were investigated, it was concluded that phalangeal QUS could discriminate between haemodialysis patients and controls, and could also discriminate between haemodialysis and osteoporotic subjects with vertebral fractures. Different characteristics of ultrasound signal could be ascribed to each bone tissue property, enabling a clear differentiation of bone tissue changes occurring in menopause, osteoporosis and azotaemic osteodystrophy [52] (Table 3).

Treatment monitoring

The QUS parameters (BTT, bone transmission time; pSOS, pure speed of sound) have shown characteristics of accuracy, stability in time, and independence of the presence of soft tissue, that enable osteotrophic treatments to be potentially followed up. In a longitudinal study of subjects on HRT therapy, Mauloni et al. [53], taking into consideration the accuracy of the method and the variations expected in time [54], calculated that an interval of 18 months between one measurement and the next is necessary. It is also possible to monitor treatment with alendronate by QUS at the phalanx and calcaneus [55, 56],

Table 3 Discrimination between dialyzed patients and control

Skeletal site	Author	No. of patients	QUS parameters	Discrimination between patients and control (p value
Phalanges	Rico [41]	23	AD-SoS	0.025
Phalanges	Przedlacki [42]	72	AD-SoS	<0.00001
Phalanges	Montagnani [40]	98	AD-SoS	<0.001
			UBPS	<0.001
Phalanges	Pluskiewicz [43]	30	AD-SoS	<0.0001
Phalanges	Pluskiewicz [44]	220	AD-SoS (females)	<0.00001
			AD-SoS (males)	<0.001
Phalanges	Guglielmi [50]	57	AD-SoS	<0.05
			BTT	<0
			SOS	<0
Tibia	Foldes [51]	71	SOS	<0.001
Calcaneus	Montagnani [40]	98	SOS	<0.05
			BUA	<0
			Stiffness	<0
Calcaneus	Arici [48]	39	BUA	<0.001
			SOS	0.014
Calcaneus	Peretz [47]	30	BUA	0.03
			SOS	0.03
			Stiffness	0.003

AD-SoS=Amplitude-dependent speed of sound, UBPS=Ultrasound Bone Profile Score, SOS=speed of sound, BUA=broadband ultrasound attenuation

and evidence of positive effects of therapy with raloxifene was demonstrated with QUS at the phalanx [57]. Measurement at the phalanx has also demonstrated and effect of treatment with residronate in a longitudinal study of patients with rheumatoid arthritis [58]. Similar studies with QUS at the calcaneus have shown that the method is able to detect the effects of treatment with calcitonin or HRT after 2 years [59, 60]. A recent study identified certain QUS parameters, such as BTT and fast wave amplitude (FWA), as effective in monitoring treatment with teraparitide, whereas QUS at the calcaneus did not detect significant variations in the follow-up period [61] (Table 4).

Even if certain evidence of the effectiveness of QUS in monitoring osteotrophic treatments is available in the literature, according to the ISCD Official Positions [28], QUS cannot be recommended for the monitoring of treatment response in patients with osteoporosis, probably because of the lack of large-scale studies describing the efficacy of QUS in monitoring the effects of treatments. It is by the way important to observe that, as the effect of different treatments can affect trabecular and cortical bone differently, this aspect suggests the possibility to monitor the effect of different treatments by means of a different QUS device. As an example, the effect of teriparatide has been shown to affect particularly the cortical bone, and this probably explains the failure of calcaneus QUS to detect changes in trabecular bone tissue following teriparatide treatment [61].

Ten-year fracture risk

The important clinical consequence of osteoporosis is the fractures that result. The main interest is therefore in the prognostic use of bone density measurements, i.e., their ability to predict the future occurrence of fractures. Even if the diagnosis of osteoporosis in terms of BMD is made in the proximal femur by DXA [62], intervention thresholds can also be based on fracture probability derived from clinical risk factors. Several such factors for fracture, with and without BMD, allow a more accurate stratification of risk than the use of DXA BMD alone. Intervention is best targeted to those in whom fracture probability exceeds a threshold of reversible risk, based on cost-effectiveness [63].

Because the QUS techniques do not involve ionising radiation and could provide some information with respect to the structural organisation of bone in addition to bone mass, there is much interest in their use; these techniques cannot be used to diagnose osteoporosis, but they can be used for the assessment of fracture risk in elderly women [64].

Table 4 Main longitudinal studies on treatments monitoring

Author	Site	Treatment	Follow-up time (years)	QUS parameters	% Changes over follow-up period
Mauloni et al. [53]	Phalanges	HRT	4	pSOS	1.5*
				BTT	10.6*
Ingle et al. [55]	Phalanges	Alendronate	2	pSOS	1.0*
				BTT	6.0*
Agostinelli et al. [57]	Phalanges	Raloxifen	4	AD-SoS	-0.15
				UBPI	-2.90
Frost et al. [60]	Calcaneus	HRT	2	Stiffness	2.9*
Gonnelli et al. [56]	Calcaneus	Alendronate	4	Stiffness	9.0*
				SOS	1.2*
				BUA	1.9*
Gonnelli et al. [59]	Calcaneus	Calcitonin	2	Stiffness	2.12*
Gonnelli et al. [61]	Phalanges and calcaneus	Teriparatide	1	BTT	-16.4*
				FWA	17.5*
				Stiffness	0.1

* $p<0.05$
pSOS=pure speed of sound, BTT=bone transmission time, AD-SoS=amplitude-dependent speed of sound, UBPI=Ultrasound Bone Profile Index, SOS=speed of sound, BUA=broadband ultrasound attenuation

Recently, Kanis et al. [65] have published tables for calculating fracture risk at 10 years by means of QUS at the phalanx, thus identifying the criteria for risk assessment based on QUS at the phalanx and age.

In conclusion, once an appropriate cost-effective threshold of probability of fracture is identified for pharmacological intervention, specific algorithms combining instrumental (DXA or QUS) and clinical risk factors should be used to identify women to be treated to avoid future fracture (Table 5).

Children

Reference data for children are the initial requirement to test the usefulness of QUS in this field, since reference curves for QUS variables may be a useful tool to assess the bone status of an individual in comparison with the reference population, and to examine the trajectory of QUS in longitudinal studies. Normative data for QUS at the calcaneus (available only for children over 6 years) [66, 67], proximal phalanges of the hand [4, 68, 69], tibia (mid-shaft) [70, 71] and radius (distal third) [72] have been established in European and American children. A large reference database according to the main anthropometric findings, including pubertal stages and body mass index, expressed as centiles, has been provided recently for phalangeal QUS [4].

The clinical use of reference curves lies in the ability to calculate the Z-score for QUS according to the main anthropometric parameters, which has an important impact in assessing skeletal status [6]. A Z-score below −2.0 could

Table 5 10 years probability of clinical vertebral fracture in European women in relation to age and AD-SoS Z-score [65]

Age (years)	+2 Z-sc	+1 Z-sc	0 Z-sc	-0.5 Z-sc	-1 Z-sc	-1.5 Z-sc	-2 Z-sc
50	0.4	0.7	1.2	1.5	2.0	2.6	3.3
55	0.6	1.0	1.7	2.2	2.8	3.7	4.8
60	0.9	1.5	2.6	3.4	4.4	5.6	7.3
65	1.2	2.0	3.4	4.4	5.7	7.3	9.5
70	1.4	2.3	3.9	5.1	6.6	8.5	10.9
75	1.6	2.7	4.5	5.9	7.6	9.7	12.5
80	1.7	3.0	4.9	6.4	8.2	10.5	13.4

The probability of sustaining a clinical vertebral fracture in the next 10 years is reported for a patient of a certain age and a certain AD-SoS Z-score

identify a condition of "low bone mineral status" according to the anthropometric variable considered, as suggested for DXA measurements by the International Society for Clinical Densitometry [73]. A large number of clinical studies on QUS in paediatric diseases have been conducted with interesting results. Some studies demonstrated that a reduced value of a QUS variable, both velocity- and attenuation-based, is associated with a reduced bone mineral status in children with disturbances of growth or disorders affecting bone health [6]. QUS and DXA parameters, measured at different skeletal sites, showed similar results, suggesting that both methods are able to identify a reduced bone mineral status [6]. Furthermore, it has been shown that in an otherwise healthy paediatric population [74, 75], and in children at risk of osteopenia [5], QUS measurements detected a reduced bone mineral status in children suffering fractures. Fielding et al. [76], using calcaneus QUS, demonstorated that a value of BUA Z-score <-2 proved to be as sensitive as a spinal DXA BMDa Z-score <-2 in identifying children with prior low-impact fractures. Similar data were found by Schalamon et al. [74] and by Baroncelli et al. [5] measuring AD-SoS at phalanges of the hand and spinal BMDa and BMD volume by DXA (Table 6). Moreover, Hartman et al. [77], in severely handicapped institutionalised children and adolescents, found that tibia SoS Z-scores correlated negatively with the presence of previous fracture (Table 7).

These results suggest that, in children, QUS could be used to an extent similar to measurement by DXA to estimate bone mineral status and bone fragility. It must also be borne in mind that QUS parameters are influenced not only by bone density, as occurs for DXA, but also by bone structure and composition, so that, in comparison to DXA, they give additional information on bone quality [13]. The present position of QUS methods in the diagnosis of a reduced bone mineral status in children should be considered as similar to that of DXA, and QUS measurements may be a viable initial screening method for osteopenia in children [6].

The Paediatric Positions of the International Society for Clinical Densitometry [28] completely leaves out all such studies and clinical experiences on QUS technique applied to children, referring only to scientific literature on X-ray-based methods, forgetting the great opportunity of using the safest methods to assess skeletal status in paediatric populations who need more care concerning the risk associated with X-ray doses.

Neonates

Premature restriction of the *in utero* process of bone mass accretion and a greater *ex utero* need for bone nutrients predisposes the preterm infant to adverse bone health [7]. Current methods of assessing bone health in the neonate have a low specificity, and the increasing survival rate of very low birth weight (VLBW) preterm infants [78] has made it necessary to explore novel, reliable, non-invasive methods for assessing bone health in these patients in recent years. The only available devices for measurement in newborns and premature children are the DBM Sonic Bone Profiler (IGEA, Italy), which has been adapted to measurement of the humerus and metacarpal bones, and the Omnisense (Sunlight Medical, Israel), which measures the radius and the tibia.

All studies hitherto conducted found that QUS parameters were significantly lower in preterm infants compared to term infants, and a significant correlation was recorded with gestation ($r=0.4–0.84$, $p<0.05$) [7, 79]. While the two ultrasound devices commonly used for this purpose are technically different, the trend in outcome is similar for each device. There is a difference between preterm and term infants at birth, and a decrement in SOS occurred when measured longitudinally in preterm infants [80–82]. These QUS changes may reflect the halt in bone mineral accrual following premature birth, a subsequent increase in cortical porosity and bone loss due to factors such as immobility, inflammation and drugs, but this requires further investigation. Ritschl et al. [80] performed QUS in term infants over the first 18 months of life, and in preterm infants from birth to 14 months, and described a decrease in metacarpal SOS from 1 month old, reaching a nadir at 6 months in term infants; in the preterm infants

Table 6 Fracture discrimination in healthy and pathologic paediatric subjects

Author	N (fx/non-fx)	QUS parameter	Fractured	Fracture free	ROC	t-test
Baroncelli et al. [5]	52/83		Mean	Mean	-	<0.0001
		AD-SoS Z-sc	-2.3	-1.5		
Schalamon et al. [74]	50/154		Mean ± SD	Mean ± SD	-	<0.05
		AD-SoS	1,914±43	1,928±39		
Fielding et al. [76]	42		-	-	AUC	<0.05
		SOS			0.84	<0.05
		BUA			0.84	

AD-SoS=amplitude-dependent speed of sound, SOS=speed of sound, BUA=broadband ultrasound attenuation, Z-sc=Z-score, AUC=area under the ROC curve

Table 7 Correlation between QUS parameters and gestational age (GA), weight and length at birth in preterm and term infants at birth: results of the main studies

Author	Variable	N	GA	Weight	Length
Nemet et al. [83]	Tibia SOS	44 term and preterm	R=0.78	R=0.74	
			P<0.0005	p<0.0005	
Littner et al. [82]	Tibia SOS	73 term and preterm	R=0.61	R=0.48	
			p<0.001	P<0.001	
Rubinacci et al. [79]	Humerus SOS	51 preterm	R=0.50	R=0.58	R=0.64
			p<0.0001	P<0.0001	p<0.0001
Rubinacci et al. [79]	Humerus BTT	51 preterm	R=0.48	R=0.56	R=0.59
			p<0.0001	P<0.0001	P<0.0001
Ritschl et al. [80]	Metacarpal SOS	132 term and preterm	R=0.55	R=0.52	R=0.47
			P<0.0001	P<0.0001	P<0.0001
Ritschl et al. [80]	Metacarpal BTT	132 term and preterm	R=0.84	R=0.80	R=0.76
			P<0.0001	P<0.0001	P<0.0001

SOS=speed of sound, BTT=bone transmission time

there was also a fall in metacarpal SOS, but the nadir was reached earlier and was lower in the most preterm infants. Metacarpal BTT in the same study group did not change significantly; while it remained stable in the term infants, preterm infants had an increasing BTT after birth, only reaching the age-matched term BTT values at the age of 4–6 months [80]. This emphasises that preterm infants have a different SOS trajectory from term infants. Nemet et al. [83] found a significant inverse correlation between tibial SOS at birth and alkaline phosphate serum ($r=0.59$, $p<0.005$). Six of the premature infants had a serum ALP of 1,400 IU/l and the correlation was stronger within this group ($r=0.75$, $p<0.05$) [83]. Both spontaneous movement and exercise have been related to changes in bone SOS [84]. Consistent with these results is the effect of modest daily activity in attenuating the decrease of SOS post-natally in preterm infants, as described by Litmanovitz et al. [85].

Genetics

There is strong evidence that genetic factors play an important role in the determination of bone mass throughout life [86, 87]; studies have estimated that up to 80% of inter-subject variance in bone density is attributable to genetic factors. Indeed, a recent study estimated that genetic factors were responsible for 30–40% of the variation in QUS measurements [88]. This study demonstrated that bone parameters assessed by calcaneus and digital QUS are under strong genetic influence (from 0.68 to 0.82), similar to that observed for DXA BMDa [89], and share some common genetic factors with those assessed by BMDa. Another study on monozygotic twins revealed that a relative contribution of genetic factors to skeletal status could be observed by phalangeal QUS, but a significant increase in the intra-pair difference in QUS with increasing age and onset of menopause was observed, and this suggests the importance of environmental factors in the female twin population [90].

Conclusions

The clinical experience have shown that QUS techniques are a useful tool to provide information on bone mineral status and fracture risk. Although QUS devices are based on the same physical principle, they differ in the skeletal site of measurement, precision, accuracy, measured QUS variables and normative data. Not all ultrasound techniques have reached a significant and sufficient level of knowledge to be applied with reliability in the clinical setting; careful review of the literature can help the clinician to take into account this aspect. However several studies in recent years have, in general, defined and confirmed the role of QUS techniques as useful tools in the assessment of bone status in a large variety of situations and pathological bone conditions. The method can be applied not only to the adult population, women and men, but also children, newborns and preterms infants.

In recent periods basic science studies have tried to solve most of the issues related to QUS technique [91], leading to an important development of the method [92], including the possibility, in the future, of generation of micro-QUS imaging methods as tools for measuring specific aspects of bone quality [91]. When the new technologies are available in the clinical practice, further improvement in the efficacy of QUS methods in the management of osteoporosis will be warranted.

Acknowledgments The authors would like to thank Francesca De Terlizzi, MSc., Scientific Department IGEA S.p.A., Italy, for her assistance with manuscript preparation.

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