Quantitative ultrasound of bone: calcaneus

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Summary

In the last 25 years, several non-invasive techniques based on the attenuation of ionising radiation have been developed to quantify bone mineral density in the axial and peripheral skeleton. They represent valid methods for determination of BMD and explain about 60-80% of the variation in bone strength. However, they provide only limited information on bone structure and on bone material properties. Quantitative ultrasound (QUS) methods have been introduced for the assessment of skeletal status in osteoporosis. The physical interaction of ultrasound and bone is complex, and not completely understood; however, it is considered that QUS provides information both on bone mass and structure. QUS, because of the lack of ionising radiation, relative portability of the equipment, ease of use, and low cost, has been marked success around the world, though it has been approved only in 1999 by FDA for clinical use in USA. The relative contribution to bone assessment of both ultrasound and the current gold standard method for bone assessment, dual x-ray absorptiometry (DXA), is still to be determined; nevertheless, QUS has demonstrated that it is able to detect bone fragility as well as DXA. Further studies needed on the diagnosis of osteoporosis using ultrasound, because current diagnostic threshold designed by the World Health Organization, cannot be always applied to QUS parameters. A better option for QUS would be to report results in terms of fracture risk, keeping in mind that a risk estimate depends not only on QUS or DXA measurement, but also on clinical risk factors.

KEY WORDS: quantitative ultrasound, bone quality, speed of sound, broadband ultrasound attenuation.

Introduction

The measurement of bone density has became an established method to determine the skeletal status for diagnosis and treatment of osteoporosis. Diagnosis of osteoporosis today is based mainly on this measurement since bone density at various anatomic sites has been found to be strongly associated with future fractures. However, both epidemiological and interventional investigations have identified risk factors for fracture other than bone mass. In particular it has been demonstrated that bone structure may play an important role in the determination of fracture. Therefore the ideal diagnostic device should be able to measure bone fragility, whatever the cause is, and not just any decrease in bone mass. QUS seems to provide information that is partly independent from bone density and is able to predict osteoporotic fractures. QUS offer the advantage of small size, relatively quick and simple measurements, no need of ionising radiation and low cost. For these characteristics, QUS has continued to be of interest in the last two decades; in 1999, the United States Food and Drug Administration approved five different ultrasound instruments for the routine diagnosis of osteoporosis, determination of fracture risk and monitoring bone changes.

Ultrasound parameters

Ultrasound is a mechanical wave vibrating at a frequency range from 20,000 waves/s to 100,000 waves/s. The ability of most physical methods of diagnosis (quantitative ultrasound of bone in this case) to provide information on the properties of a particular medium depends on the way in which the ultrasound wave is modified by the medium. With ultrasonic propagation through bone, both the velocity of transmission and the amplitude are affected by the medium. Bone tissue therefore may be characterized in terms of ultrasound velocity and ultrasound attenuation. From this simple, fundamental starting point, it is interesting to note the variety of approach taken in implementing clinical measurements of velocity and attenuation in commercial quantitative ultrasound devices. In fact, commercial bone QUS has utilized transit time velocity measurement (the time for the arrival of ultrasound signal at the receiving transducer), with different definition: bone velocity (BV), heel velocity (HV), speed of sound (SOS). For attenuation, more uniformity is present among commercial devices; in fact attenuation is typically characterized by broadband ultrasound attenuation (BUA), the slope at which attenuation increases with frequencies, generally between 0.2 MHz and 0.6 MHz. The velocity of ultrasound wave propagation is determined by the transit time and by the width crossed, and it is expressed as m/s. Speed of sound (SOS) can be related to the mechanical properties by the equation: $SOS = (E/r)^{1/2}$, where E is the modulus of elasticity and r is the bone density expressed in gr/cm^3. Current commercial systems for studying the calcaneus use two transducers (a transmitter and a receiver), positioned on each side of the bone to be measured, and three different methods of calculating velocity have been employed: heel velocity (calcaneus + soft tissue), bone velocity (calcaneus only) and time of flight velocity (TOF) (between transducers positioned at a fixed distance and assuming a constant heel thickness). These three approaches to velocity derivation yield slightly different values, but correlate strongly with each other (1). As an ultrasound wave propagates through the bone some of its energy is lost, and this phenomenon is known as attenuation. Factors contributing to the attenuation in bone include scattering, diffraction and absorption. Absorption predominates in cortical bone and scattering in trabecular bone. The increase in attenuation as a function of the frequency is measured by comparing the amplitude spectrum for a reference material with that of the measured sample. The slope of attenuation (BUA) in dB/MHz

is given by linear regression of the spectral amplitude difference. Some manufacturers have implemented derived parameters from BUA and velocity, such as Stiffness, Quantitative Ultrasound Index (QUI), soundness and osteo sono-assessment index (OSI). The combination of BUA and SOS into a single parameter has been shown to improve precision; furthermore, from the point of view of clinical interpretation, a single parameter, which combines velocity and attenuation, can simplify interpretation.

QUS and bone

Velocity and BUA provide quantitative information on ultrasound interaction with the medium; it is currently accepted that QUS parameters are not only influenced by bone density, but also by bone structure. Theory suggests that BUA is determined by bone density and bone microarchitecture, while SOS is influenced by the elasticity of bone as well as by bone density. However, the exact mechanisms of ultrasound interaction with bone and the physical properties measured remain undetermined. Considerable data exist showing the positive dependence of attenuation and velocity on bone mineral density (2). The relationship between QUS and BMD are higher *in vitro* than *in vivo*, probably also as a consequence of the presence of soft tissue and of anatomic discordance (3); otherwise this poor association with QUS and BMD has been often attributed to the fact that QUS may measure structure. In particular it has been shown that BUA depends on the trabecular orientation (4, 5); moreover, Gluer et al. (4) have suggested that SOS is related to trabecular separation and BUA either to trabecular separation or connectivity. Other Authors did not find any relationship between histomorphometry and QUS parameters after correction for BMD (6). Nicholson et al. (7) have shown that the ability of QUS to reflect bone structure is also dependent on the direction of the measurement. Recently it has been demonstrated, in human calcaneal specimens, that QUS reflects especially BMD and to a less extent, bone microarchitecture (8). It has been also shown that SOS, after correction for BMD, is the best predictor of Young modulus, indicating that this parameter can give information on the mechanical architecture of trabecular bone (9). In cadaver studies, calcaneal ultrasound correlates with femoral and vertebral strength, but the predictive ability is less than, and it is not independent, from BMD measurements (10-11). However, in contrast to these results, Lochmuller et al. (12) found that calcaneal QUS correlates with failure load of the proximal femur similarly to femoral neck BMD.

In conclusion, qualitative evidence for the influence of structure on ultrasound exists, but there are no conclusive data demonstrating that ultrasound provides useful information on specific structural parameter at clinical sites.

Calcaneal QUS devices

Since the pioneering work of Langton et al. in 1984 (13), many clinical quantitative ultrasound machines have been developed and there are currently a multitude of different devices on the market. Ultrasound transducers are coupled to the subject either with water (wet systems) or gel (dry systems). The sites measured also vary, but most of the available devices measure the calcaneus. The calcaneus is the most studied skeletal site for QUS assessment for several reasons; the high percentage of trabecolar bone (90%), which has a turnover higher than cortical bone, allows early evidence of metabolic changes; the calcaneus is also easily accessible and the mediolateral surfaces are fairly flat and parallel, thus reducing repositioning error. The choice of the calcaneus as a test site has been supported by Black et al. (14), who reported that the calcaneus appeared to be the optimal bone mineral density measurement site in the prediction of any type of osteoporotic fracture in perimenopausal women. In Table I are reported commercial calcaneal QUS devices. Although the Walker Sonix UBA 575 is no longer available, it is listed because it provides a background for current systems and also because many studies were carried out using this system. These devices show great technological diversity: coupling, mode of data acquisition, variables, calibration method, hardware performance, analysis algorithms, transducer designs. These differences, combined with the fact that no absolute standard exists for ultrasound measurements, cause the impossibility to directly translate the clinical utility of a validated system into that of other technologically different QUS devices. Among water bath systems, the Achilles plus, available in the early 1990s, for its proved ability to predict fragility fractures and comparability to central DXA, is one of the most used ultrasound devices. Compared with water-coupled systems, gel-coupled systems, such as Sahara, have the advantage of being more portable and having fewer potential concerns about hygiene, disadvantage results from their reduced control over the measurement environment, such as the stability of the temperature and hydration of the tested heel. These factors could significantly influence the precision of the measurements. GE Lunar has recently released a newer version of Achilles called Achilles Insight: this is an imaging ultrasonometer, based on the Achilles plus, but water is contained in an inflatable silicone pad and isopropyl alcohol spray is used to provide the coupling (Fig. 1). A good agreement between Achilles plus and Achilles Insight has been recently demonstrated (15). Regarding the precision, for the same variables, there is moderate difference among different devices; in Table I are reported the values of short-term precision usually reported for each device from many studies (Table I). For QUS measurements at calcaneus sources of low precision include presence of soft tissue, thickness variation, coupling agent characteristics, repositioning error, duration of immersion of the foot and temperature (16-18). Foot positioning is considered the primary source of error in BUA measurement because of the lack of homogeneity of the calcaneus (18).

Clinical application of QUS

Although considerable effort has been made to characterize the relationship between QUS and BMD measurement of the same skeletal site, from a clinical point of view, the most important issue regarding QUS is its ability to predict fracture risk. There is ample evidence documenting the ability of calcaneal QUS to predict osteoporotic fracture risk both in women (19-34) and in men (31, 34). It is important to emphasize that QUS parameters result independent predictors of osteoporotic fracture, even after adjustment for BMD (19-24, 30). These studies reported a strong association of calcaneal QUS with vertebral fracture (19, 20, 24, 27, 32) hip fracture (21-23, 28, 33) and osteoporotic fractures in general (30, 31, 34). Logistic regression analysis has shown that the fracture risk usually increases by 1.5-2.5 times for every 1 standard deviation reduction of each QUS parameters. Moreover it has been demonstrated that the fracture risk prediction increases with both the combination of QUS and DXA (22, 24, 32).

Correlation between QUS parameters and BMD, as measured by X-ray absorptiometry have been under investigation since QUS was first introduced for clinical practice. Correlation coefficients usually range from 0.3 to 0.8 and there is general agree-

Table I - Calcaneal QUS devices.

Device	Manufacture	Trasmission	Parameter	Precision (cv) (%)
Achilles plus	GE Lunar	Water	BUA SOS Stiffness	0.8-4 0.2-0.5 1-2.7
Achilles Express	GE Lunar	Water and gel	BUA SOS Stiffness	Not available Not available 1-2
Achilles Insight	GE Lunar	Water and alcohol	BUA SOS Stiffness	1.4-3.1 0.2-0.4 1.9-2.1
CUBA	McCue	Gel	BUA SOS	1.5-4.5 0.2-0.6
DTU-one	Osteometer	Water	BUA SOS	0.8-2.5 0.2-0.4
Paris	Nordland	Gel	BUA SOS	1.8 0.3
QUS-2	Metra	Gel	BUA	0.8-2.5
Sahara	Hologic	Gel	BUA SOS QU	0.8-5.0 0.2-0.4 1-3.5
UBIS 5000	DMS	Water	BUA SOS	0.8-2.5 0.2-0.4
UBA575+	Walker Sonix	Water	BUA SOS	2-5 0.2-0.6

Figure 1 - Achilles Insight device (GE, Lunar).

ment that QUS and BMD interact differently with bone and that explains why the correlation between the two methods, even-though significant, is modest (35, 36). Since WHO has defined Osteoporosis on the basis of BMD, a sure diagnosis can be formulated only with a technique that directly measures bone mineral density, as bone densitometry. However, the usefulness of QUS is justified in numerous studies; in fact some Authors have demonstrated that QUS parameters are more predictive of bone mass than the factor risk evaluation (37, 38). In other wards, postmenopausal women who should be referred for further examination by DXA, could be selected better on the basis of QUS measurement than with risk factors evaluation alone. Moreover, published data on the cost-effectiveness of this approach are not sufficient to recommend a population screening with QUS (37, 39, 40). Moreover, guidelines on the position of QUS in the diagnosis and therapeutic decision are not available. In this respect, a crucial point is the evaluation of the possibility of using WHO criteria also for QUS, since it has been shown that QUS and DXA cannot always identify the same population (41). Some studies have shown that the cut-off of -2.5, utilised for the definition of osteoporosis with DXA, can be employed also for some QUS devices, such as the Achilles (42). On the other hand, for other instruments, different cut-offs have been calculated (42, 43). Moreover, it has been recently demonstrated that clinical risk factors are related both to QUS and DXA parameters when expressed in terms of Z-score, and that the proportion of postmenopausal women classified as osteopenic or osteoporotic is similar, with both DXA and QUS (44). At present no universal cut offs are disposable for QUS parameters and, therefore, even though good correlations have been showed between parameters obtained by different devices (45), it is not possible to standardize nor-

Table II - Calcaneal QUS and fracture.

Author	Fracture outcome	Subjects	Velocity (RR)	BUA (RR)	Derived parameters (RR)
Selected retrospective studies					
Ross,1995	Vertebral	702 women	–	1.5-1.7	–
Gonnelli, 1995	Vertebral	304 women	4.5	3.1	4.8 (Stiffness)
Schott, 1995	Hip	129 women	2.7	3.7	3.5 (Stiffness)
Thompson, 1998	All fractures	3180 women	1.5	1.4	1.5 (Stiffness)
Hartl, 2002	Vertebral	500 women			3.0 (Stiffness) 3.8 (QUI)
Ekman, 2002	Hip	99 men	1.9	1.9	2.2 (Stiffness)
Krieg, 2003	Hip	7562 women	2.5 2.1	2.3 2.4	2.7 (Stiffness) 2.4 (QUI)
	Forearm		1.6 1.7	1.5 1.7	1.6 (Stiffness) 1.7 (QUI)
	Other fractures		1.1 1.1	1.1 1.1	1.1 (Stiffness) 1.2 (QUI)
Gluer, 2004	Vertebral	2837 women	1.4-1.5	1.2-1.4	1.5 (Stiffness)
Gonnelli, 2004	All fractures	401 men	3.0	2.8	3.2 (Stiffness)
Prospective studies					
Hans, 1996	Hip	5662 women	1.9	2.0	–
Bauer, 1997	Hip Non spine	6189 women		2.0 1.3	
Pluijm, 1999	Hip Non spine	132 men and 578 women	1.6 1.3	2.3 1.6	
Stewart, 2003	Forearm All fractures	1000 women		3.25 1.39	
Huopio, 2004	All fractures	132 women	1.8	1.7	1.4
Hans, 2004	Hip	589 women	1.8-2.4	1.9-2.6	1.9-2.8 (Stiffness)
Khaw, 2004	Hip Non hip	14824 men and women	2.22 1.96	1.99 1.59	

mal range as it has been made for DXA. Moreover, QUS reference phantoms for cross-calibration procedures and standardization methods between different devices are not available. However, QUS parameters could be considered as an important risk factor, allowing to classify a subject as at "low", "medium" or "high" risk on the basis of QUS result. Ayers et al. have demonstrated that the associate evaluation of clinical risk factors and QUS shows a sensitivity in the diagnosis of osteoporosis similar or superior to the axial DXA (46); following this strategy a further DXA evaluation could be indicated only in patients with positive risk factors and normal QUS (47). A strategy combining QUS, DXA and clinical factors for the identification of women needing an appropriate treatment has been recently proposed by Hans et al. (42).

Because of the limited experience, monitoring skeletal changes solely by QUS cannot be recommended yet (35). The ability of QUS to monitor change widely depends on the reproducibility of QUS parameters and on the magnitude of the response. The time period to follow individual subjects would most likely exceed those required for bone densitometry; in fact, even though some studies showed a significant increase of QUS parameters in patients treated with antiresorptive drugs (48-50), it is not possible to identify, with QUS, change of bone status induced by these drugs, earlier than 2 years. Nevertheless, for the possible usefulness of QUS in the follow up, in order to maximize its ability to monitor change and to minimize any measurement error, adequate measurement protocols and quality assurance procedures are needed.

The use of calcaneal QUS has also been proposed in secondary osteoporosis, such as osteoporosis induced by corticosteroids (51, 52) or associated with rheumatoid arthritis (53). In a recent study, the influence of corticosteroid therapy on QUS parameters during the first year after renal transplantation has been investigated (54). The ability of QUS to give us information on both bone mass and qualitative characteristics of bone could be utilized also in the diagnosis of different metabolic bone diseases, such as primary and secondary hyperparathyroidism (55, 56). QUS at calcaneus has been employed also in patients with osteogenesis imperfecta (57) or with Sudeck's disease of bone (58).

Conclusions and future perspectives

A substantial body of knowledge regarding the performance of QUS techniques has been gathered. To date, evidence sup-

ports the use of QUS for the assessment of fracture risk. Additional clinical applications of QUS, as the assessment of rates of changes for monitoring disease progression or response to treatment, require further investigation. Moreover, QUS technology has tremendous potential for further improvement and refinement. If one takes an optimistic view, it may eventually be possible to develop a truly non invasive method that will allow the investigation of relevant characteristics of skeletal status that can only be studied by invasive histomorphometric methods today. QUS may also improve the evaluation of skeletal properties on a micro level and open new frontiers for more in-depth and more comprehensive investigation of bone metabolism, including the effect of therapeutic interventions. Currently, the low cost of the devices makes them very attractive and this has led to their rapid dissemination in many countries. In the future, the potential for developments beyond bone densitometry may represent an additional promoting factor. QUS will probably play a dominant role in the assessment of osteoporosis and potentially other skeletal disorders as well.

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