QUS in bone: non-calcaneal skeletal sites in adults

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Summary  
Quantitative ultrasounds (QUS) have been developed as an attractive alternative to current radiation-based bone densitometry techniques in the management of osteoporosis. Depending on the QUS devices investigated, various skeletal sites have been studied. In this mini review we will mostly focus our interest on the finger phalanx, the radius and the tibia. Well established and validated normative reference curves, allowing the monitoring of bone loss through age, exist. From various studies, QUS seem to be an effective method in the identification of “DXA osteoporosis”. Furthermore QUS are also able to discriminate any type of osteoporotic fracture (e.g. hip, vertebral and/or forearm fractures) from controls. Similar results were found for the discrimination of patients with secondary osteoporosis. Very few prospective studies on fracture were performed at the non-calcaneal skeletal sites. Unfortunately, results are somehow contradictory. Promising results have been reported concerning the treatment monitoring although mostly based on small open label studies. Therefore use of ultrasounds can be advocated to obtain additional experience with regard to longitudinal measurements of disease progression and impact of treatment. In the face of current lack of consensus agreement on how results of QUS devices should be interpreted in order to diagnose osteoporosis, it would be reasonable to consider QUS parameters as an additional clinical factor to be taken into account in the management of osteoporosis.

KEY WORDS: quantitative ultrasounds, phalanges, radius, osteoporosis, fractures.

Introduction  
Osteoporosis is a systemic skeletal disease characterized by a reduction of bone mass and microarchitectural deterioration of bone tissue resulting in a reduction in bone strength with a consequent increase in bone fragility and susceptibility to fracture (1). In the last 30 years, several non-invasive techniques based on the attenuation of ionizing radiation, such as the dual-energy X-ray absorptiometry (DXA), have been developed to quantify Bone Mineral Density (BMD) in the skeleton. However, they provide only limited information on bone structure and bone material properties (2). Quantitative ultrasounds (QUS) have therefore been developed and are an attractive alternative to current radiation-based bone densitometry techniques as they are non-invasive, relatively inexpensive, portable and, most importantly, free of ionizing radiation. Furthermore, information concerning bone structure as well as density can be provided (3).

Many skeletal sites have been explored such as the calcaneus, phalanx, radius, tibia, patella (4-7), metatarsus (8) and ulna (9, 10). However, most of these sites are not as yet used in a routine clinical setting but only for research purposes. In this mini-review, we will mostly focus our interest on skeletal sites used in clinical routine practice, except for the calcaneus which is covered elsewhere. It is important to remember that performance of one device cannot be extrapolated to another one technically different. Therefore, the reader should be cautious while interpreting the data.

Clinically investigated sites  
For an appropriate measurement with QUS it is important that the skeletal sites investigated are easy to access, relatively free of soft tissue, and clinically relevant.

Finger phalanx  
The finger phalanx measurement site is the distal metaphysis of the first phalanx of the last four fingers. The mediolateral surfaces are approximately parallel, thereby reducing ultrasound scattering. In the metaphysis, both cortical and trabecular (around 40%) bone are present (11, 12). The metaphysis of the phalanx is also characterized by a high bone turnover (bone tissue at the phalanx shows the highest sensitivity to bone resorption occurring at the menopause) (13).

Radius  
Measurement sites have been restricted to the peripheral skeleton due to the high attenuation nature of ultrasound. However, with the advent of axial transmission techniques, the accessible sites now include many others such as the radius with cortical bone. The radius is studied by techniques of longitudinal transmission of the ultrasound wave. This site was chosen, amongst others, for its high reproducibility, that is, good precision, and the fact that forearm fractures are known to be osteoporotic fractures.

Tibia  
The mid-tibia is chosen due to its long, straight and smooth surface. Furthermore, the overlying soft tissue is very thin.
thereby minimizing errors in the Speed Of Sound (SOS) measurement (14). Since 80% of the skeleton is comprised of cortical bone, which could be involved in osteoporotic fractures, it may be of clinical interest to measure a weight bearing bone cortical bone such as the tibia. In addition, cortical bone loss may play an important role in determining whole-bone strength. Measurement at this site is of the longitudinal ultrasound velocity along the anteromedial cortical border of the mid-tibia. Propagation occurs mostly along the external surface of the bone, and therefore provides information mainly on the cortical bone tissue. Investigation of the tibia and radius is sensitive to phenomena of endosteal resorption (15).

Non calcaneus quantitative ultrasound devices

Manufacturers have released a great variety of commercial devices for QUS assessment at peripheral measurement sites (16-19). Mostly two non-calcaneus devices are commercially available on the market for measurements:

- The DBM Sonic 1200 or Bone Profiler - BP (IGEA, Carpi, Italy).
- The Omnisense® 7000S bone sonometer (Sunlight Medical systems, Tel Aviv, Israel).

The DBM Sonic Bone Profiler (Fig. 1): transverse transmission

This device performs Quantitative Bone Ultrasonography at the (proximal finger) phalanges. It is the only ultrasound device that applies the method of signal analysis in transmission through phalanges. It uses a fixed-point transmission technique to measure amplitude-dependent ultrasound velocity through the proximal phalanges of the last four fingers of the hand. Two 12-mm diameter, 1.25 MHz transducers are assembled on a high-precision caliper (± 0.01 mm) that measures the distance between the probes. The probes are positioned on the mediolateral surfaces of the distal metaphysis of the phalanx using the phalanx condyle as reference point. Coupling is achieved by using standard ultrasound gel. The investigated parameters are the AD-SOS, the UBPI and the BTT (Fig. 1).

- AD-SOS: velocity can be measured using either the axial or transverse transmission modes of propagation (20, 21). When normal bone is tested, the amplitude of the first signal received is above the predetermined threshold, but for osteoporotic bone, significant attenuation occurs and the Amplitude of the first signal is not enough to trigger the reading. The velocity thus measured is amplitude related, hence the Amplitude-Dependent Speed Of Sound (AD-SOS). This enables the differences in SOS measured between normal and osteoporotic bone to be magnified. The SOS is expressed in m/s.
- Fast wave amplitude (FWA, in mV) is the maximum amplitude of the fastest peak of the received US signal.
- Signal dynamic (SDy, in mV/ms²) expresses the second derivative of amplitude versus time of the fastest peak of the received US signal and represents the sharpness of the peak reflecting its frequency content.
- Bone transmission time (BTT, in ms) is the time width of the US received signal and is calculated by subtracting the instant corresponding to the arrival time of the fastest US received signal from the time of transmission of a US pulse at 1700 m/s velocity.

These three latter parameters are combined into one index named Ultrasound Bone Profile Index (UBPI) or Ultrasound Bone Profile Score (UBPS) using the formula (20): UBPI = 1/1+exp((-0.00186 SDy(mV/m²) - 0.0566FWA(mV) - 1.14676BTT(ms) +3.03)). The UBPI can be considered first as a measure of the quality of the trace (22). It also enables the quantification of the modifications encountered by the ultrasound signal in passing through normal and osteoporotic bone tissue. However, its clinical role remains unclear.

The Omnisense® Bone Sonometer (Fig. 2): axial transmission

While most of the commercialized ultrasound devices measure only single pre-defined peripheral skeletal sites with little overlying tissue (i.e., calcaneus, phalanx, or tibia), the Omnisense ultrasonometer can measure bone at multiple skeletal sites, including the distal 1/3 radius (forearm), phalanx (finger), tibia (lower leg) and metatarsus (foot). Measurement at additional skeletal sites enables testing of bones with different combinations of cortical and cancellous bone content and weight-bearing and non-weight-bearing bone, and thus provides a potentially more comprehensive analysis of the skeleton. This device measures the acoustic velocity (Speed Of Sound – SOS) in axial transmission mode along the cortex. SOS represents the...
velocity of ultrasound transmission usually averaging over paths through bone and soft tissue and is expressed in m/s. The Omnisense comprises a desktop unit and a family of small, hand-held probes designed to measure various skeletal sites (15, 23). Each probe contains a set of transducers housed tightly together in a compact holder. The different probes are designed to operate at different SOS ranges, under different soft tissue thickness conditions, and to measure various bone types. The hand-held probes are connected by a cable to the Omnisense main unit. During measurement, a probe is applied directly to the skin at the measured site. A thin layer of standard ultrasound gel is applied between the probe surface and the skin to facilitate good acoustic coupling. Inaudible high frequency acoustic waves, at a center frequency of 1.25 MHz, are produced by two transducers (called ultrasound signal generators or transmitters) in the probe. The ultrasound waves are conducted along the bone and then detected by two different transducers (called ultrasound signal detectors or receivers) in the same probe.

Normative data

Monitoring changes in bone is an essential part of osteoporosis management. Bone mass and bone strength increase throughout childhood to a peak in mid-life. A decline in bone strength follows, commencing at age 40, but picks up speed only later on in life. Bone mass declines drastically after menopause with the loss of the protective effect of estrogen on bone. To express these changes, QUS results can be expressed in absolute values or in T and Z-scores thanks to well established and validated normative reference curves (figures 3 and 4), allowing bone loss to be followed with time (8, 24-28). Some studies used these results to express bone loss through age, and mostly through the menopause (8, 14, 25, 29-38).

What are we measuring? In vitro studies

Most of the studies have been conducted on the calcaneus or trabecular bone. Although about 80% of the ultrasound parameters are explained by bone mineral density when site matched comparison is performed (39-42), the remaining 20% are related to bone quality and other bone properties (e.g. microstructure, elasticity, anisotropy, connectivity, porosity) (3, 16, 18, 24, 43-58). The combination of these parameters with the bone density would estimate the overall bone strength which is a crucial parameter in case of fragility fracture. It has been proven that QUS are strongly related to bone strength and are therefore a good predictor of osteoporotic fracture (45, 59-70).

These considerations cannot be so easily extrapolated to the phalanx, tibia and radius as the measurement and the bone nature are different although similarities have been observed. At the cortical site, SOS seems to be more influenced by min-
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QUS at the calcaneus are good in discriminating patients with osteoporotic fracture from normal subjects (2, 35, 57, 74, 92, 96-106). Indeed, many cross-sectional studies have shown that patients with fractures have lower ultrasound values than patients without fractures, and that the fracture risk discrimination by QUS is as strong as for absorptiometric techniques such as Single-energy X-ray absorptiometry (SX A) and DXA (102-109). Overall, axial and transverse transmission in cortical bone show only minor performance compared to transverse transmission in trabecular bone such as the calcaneus. However, this slight difference between the skeletal sites in a patient’s discrimination depends on the type of osteoporotic fracture.

Concerning the discrimination of any type of fracture, Barkmann et al. compared women who had previously suffered from a fracture of the hip, spine, ankle, or forearm to healthy women without fracture (15). They found that the sites showed significant fracture discrimination with age-adjusted standardized Odds Ratios (ORs) for the phalanx and radius which ranged from 4.1 to 4.5 and AUCs from 0.88 to 0.89. Similarly, Damilakis et al. studying the discriminative ability of the SOS concerning fractures at the wrist, vertebrae, and ribs, found high phalangeal and rib SOS (21). Hanes et al. studying the discriminative ability of the SOS in multiple bone sites (only distal 1/3 radius, 105, 109, 112-119).

Concerning hip fracture, the discrimination ability of QUS at the phalanx, tibia, and radius is only slightly less significant than that of the calcaneus with an OR around 2 (20, 34, 57, 58, 86, 105, 109, 112-119).

Hans et al. studied multiple bone sites (only distal 1/3 radius, third phalanx and ultradistal radius are considered here) on the discrimination of hip fractures (21). Discrimination with SOS at all ultrasound sites was highly statistically significant (age and BMD-adjusted ORs per SD decrease = 1.4-3.0; AUC ranged from 0.77 to 0.92). Distal one-third radius measurement (OR equal to 2.4, with the AUC equal to 0.92) was the best discriminator of hip fracture patients from controls, although results were not statistically better than those of the other sites. Weiss et al. demonstrated the ability of the SOS at the radius (distal 1/3 of the radius) to assess hip fracture risk in elderly women (120). The OR per standard deviation (SD) decrease of SOS was 2.16 (1.46-3.19) and the AUC of 0.79 (0.73 - 0.86). In 2004, Damilakis et al. found, for the SOS at the phalanx, a significant OR equal to 2.63 and an AUC equal to 0.74 which was better than the results reported on the calcaneus in the same study (121). On the contrary, Ekman found that QUS of the fingers phalanges cannot discriminate hip fracture patients from controls (113). Tibial QUS have proven to be reliable in discriminating osteoporotic hip fracture risk at an early stage in the adult population with diseases or pharmacologic treatments influencing bone metabolism (122, 123).

Studying vertebral fractures, Knapp et al. found that SOS at the phalanx and radius (but not tibia) had a good discriminative power (37). The OR per SD decrease in SOS was 2.0 (1.22 to 3.23) for the phalanx, 1.4 (1.03 to 1.99) for the radius and 1.2 (0.87 to 1.66) for the tibia. The PhOS study, performed on 10,000 women, also demonstrated the effectiveness of QUS at the phalanx in discriminating women, obtaining an OR for AD-SOS of 1.7 (C.I. 1.5-1.8) (20). The same conclusion was given...
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by Guglielmi et al. with an age-adjusted standardized OR being similar for AD-SOS at the phalanx (distal metaphysis of the proximal phalanx) and DXA (OR = 1.8 and 1.5 respectively) (124). They later found that the age and BMI-adjusted OR ranged from 2.0 (AD-SOS) to 3.1 (UBPI), compared to 4.1 for BMD by DXA (77). The Basel Osteoporosis Study demonstrated that the discriminative performances of the phalanx was comparable with the results obtained with axial DXA (89). However, in a study, only UBPI (and not AD-SOS) was found to be able to discriminate patients (125).

The use of phalangeal QUS may predict risk of fracture of the adjacent forearm, extending the use of QUS in predicting risk of fracture of the hip based on measurement of the calcaneus and the tibia (118, 122, 126, 127). Knap et al. shown that semi-reflection ultrasound measurements in cortical bone at the phalanx and radius (but not tibia), using the SOS, were able to discriminate Colles-fractured women, although the ORs were lower than with lumbar spine and proximal femur BMD by DXA (128). The age-adjusted ORs were 1.50 (95% CI 1.07-2.10) for the radius, 1.23 (0.86-1.76) for the tibia and 1.85 (1.06-3.23) for the phalanx.

Secondary osteoporosis

QUS are also able to discriminate patients with secondary osteoporosis compared to controls in the case of osteoporosis induced by thyroid disease (129), primary hyperparathyroidism (130-133), glucocorticoid excess (136, 137), lactose intolerance (138), rheumatoid arthritis (139-143), osteogenesis imperfecta (144), osteoporosis in the elderly (145), osteomalacia (146), hyperparathyroidism (147-150), epilepsy (151, 152), osteogenesis imperfecta (153), Cushing’s syndrome (154), bone marrow transplantation (155), calcium stone disease (156) and diabetes mellitus (157).

Ability of QUS to predict osteoporotic fracture

Many prospective studies have shown that fractured patients have lower calcaneal ultrasound values than normal patients and that QUS parameters are consistently predictive of osteoporotic fractures (5, 100, 101, 157). It is accepted that calcaneal SOS, BUA or stiffness double the hip fracture risk for each decrease in standard deviation (100, 101, 103, 157-160). Very few prospective studies were performed at the non calcaneus skeletal sites. Mele et al. found values of relative risk of 1.5 (C.I. 1.1-1.7) for AD-SOS in evaluating low-energy peripheral fractures (92). However, the number of fractured patients was very few (8). The prospective Osteoporosis and Ultrasound Sound Study (OPUS), performed on more than 2,000 post-menopausal women, revealed that AD-SOS and UBPI measurements at the phalanx are predictive clinical low trauma fractures as well as measurements by central DXA (161). These results have not been confirmed for the prediction of hip fracture in a large cohort such as the SEMOF (more than 7,000 elderly women). Indeed, a non-significant relative risk of hip fracture prediction has been reported (162). However, the study has been performed on the first ultrasound generation system, the DBM 1200, and it has been made known that the cause of the negative outcome could be due to technical problems linked to the ultrasound trace analysis. This is now corrected in the new IGEA Bone Profiler system. Similarly, the prospective Basel Osteoporosis Study (BOS) study reported negative results concerning the prediction of vertebral fracture by the phalangeal ultrasound (163). So far, no prospective studies have been reported for the radius and the tibia.

Treatment effect and monitoring

Cross-sectional studies demonstrated that QUS can differentiate between subjects using HRT and age-matched controls, and between subjects suffering from bone-affecting diseases and age-matched controls. Women undergoing HRT had higher SOS, AD-SOS or SOS values at multiple skeletal sites than age-matched controls, although only the radius and tibia SOS reached statistical significance; a clear effect of the duration of HRT use was seen for the phalanx measurements, the differences being less marked elsewhere for these subjects and demonstrating the protective effect of ERT on bone (22, 36, 38, 93, 164, 165).

The fact that QUS can also monitor the effect of osteotrophic treatments has been repeatedly demonstrated in small open label prospective studies for measurements at the phalanx and the radius. Large double-blind placebo-controlled studies are, however, lacking. QUS were shown to be effective in longitudinal monitoring of postmenopausal bone status and in the follow up of pharmacological and non-pharmacological osteotropic therapies (166-170). A positive effect on bone due to treatment with Alendronate over 12 months was detected by QUS. The treatment group showed a significant increase in T-score at two out of four skeletal sites measured prior to and following the commencement of treatment (171). Due to their characteristics of high long-term stability and independence on arthropathy and soft tissue quantities, BTT and pure Speed Of Sound (pSOS) have shown better performances in monitoring of osteotrophic treatments such as Alendronate, HRT and Risedronate (172) (170) (173). Similar results were found at the tibia (174). Indeed, post-menopausal women with T-scores of -2 or less at one site were recruited and treated with Alendronate for at least 1 year. QUS values increased significantly (0.21 ± 0.09 T-score, p = 0.02 with (0.03, 0.39)) after 12 months; a significant increase in mean T-scores was also demonstrated at all sites assessed according to baseline T-score of -2 or less.

Conclusion

Over the past 15 years, a substantial body of knowledge regarding the performance of QUS techniques has been gathered. To date, less prospective evidence supports the use of non-calcaneum QUS techniques for the prediction of fracture risk in elderly women. However, cross-sectional studies have demonstrated close associations between QUS parameters and osteoporotic status. Therefore, one can foresee that ultrasound techniques may have the potential for preventive screening for osteoporosis. Unfortunately, due to the ambiguities in assessing accuracy of QUS, currently there is no consensus agreement on how results of QUS devices should be interpreted in order to diagnose osteoporosis. Nevertheless, the recommendation prone by the British National Osteoporosis Society (NOS) (175) seems to be reasonable and adequate:

- A low QUS value constitutes an independent risk factor for osteoporotic fracture in postmenopausal women.
- A low QUS value constitutes an indicator of low bone mass more important than clinical risk factors.
- Patients with low QUS values can be prescribed a further BMD test or a therapeutic regimen if other clinical risk factors are present.

Due to limited experience, monitoring of skeletal changes solely by means of QUS cannot as yet be recommended. Depending on the devices and the skeletal sites, the time periods to follow individual subjects would apparently exceed those recommended.
quired for bone densitometry. However, it is important to note that when using the standardized precisions, difference between DXA and QUS are smoothed. The overall performance, mostly based on the values of ORs of non calcaneus QUS devices is not as good as the one reported for certain calcaneus QUS devices. However, these ORs do not take into account the biological range of the device. Maybe by standardizing the OR as we do for the precision would give us a different regard on the results of non calcaneus QUS devices. This should be further investigated. Limited longitudinal sensitivity is a lesser issue for studies on groups of subjects in research settings. Here, use of ultrasound can be advocated to obtain additional experience with regard to longitudinal measurements of disease progression and impact of treatment, and potentially differential changes between BMD and QUS parameters.

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