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 contradictories. 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 consensual agreement on how results of QUS devices should be interpreted in order to diag-

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, transportable 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

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).

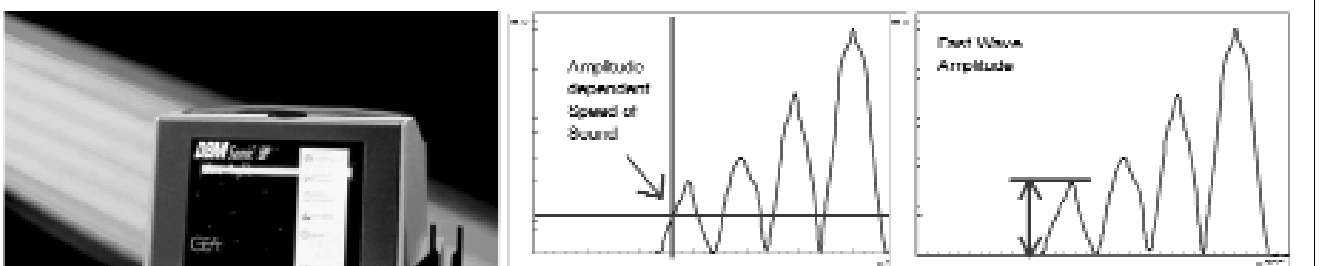
The DBM Sonic Bone Profiler (Fig. 1): transverse transmission

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) +3.0)]. 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



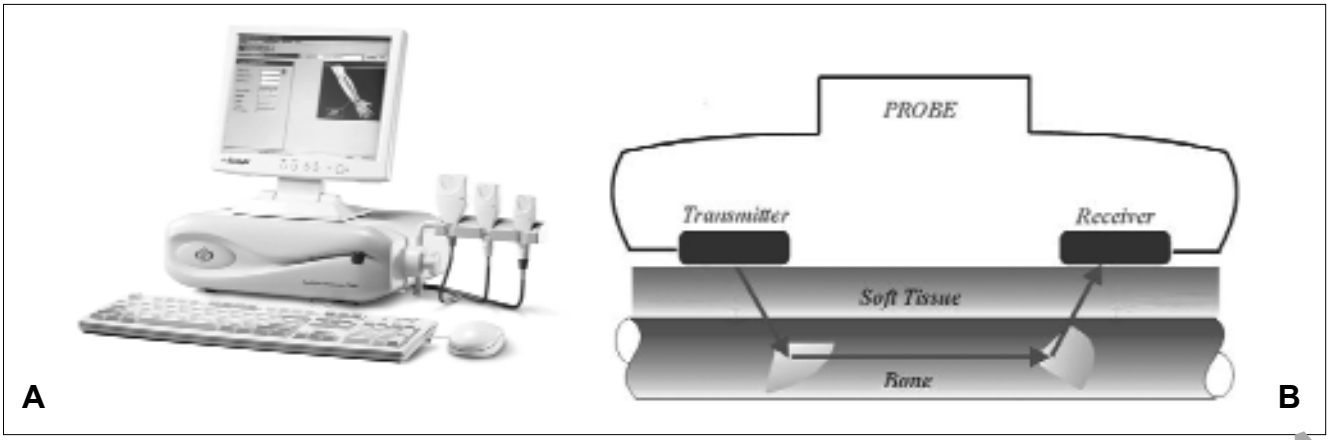


Figure 2 - The principle of the Sunlight's Omnisense® Bone Sonometer: axial transmission. A) main unit and the 3 different probes for multi-site measurements. B) illustration of Sunlight's axial transmission technology which transmits ultrasound waves along the bone.

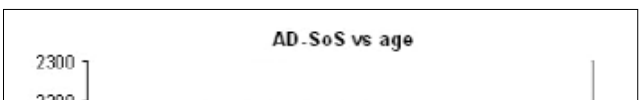
velocity of ultrasound transmission usually averaging over paths through bone and soft tissue and is expressed in m/s. The Omnisense comprises a desktop unit and a family of small, hand-held probes designed to measure various skeletal sites (15, 23). Each probe contains a set of transducers housed tightly 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.

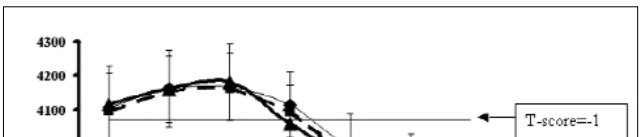
Normative data

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-





eral density than the elastic characteristics of bone (45, 53, 57, 60, 71-74). However, QUS at these non-calcaneus sites are also correlated to other bone properties. The bone architecture of the phalanx influences the SOS, the form (number of peaks) and the Fast Wave Amplitude of the ultrasound signal (12). The SOS is also influenced by the cortical area, cortical porosity and density, while the amplitude of the QUS signal is influenced mainly by the area of the medullar canal (12, 75-78). Cortical thickness, an index of bone resistance, and relative cortical area are known to be quantities of primary importance in determining the moment of inertia and thus the load resistance of the bone in question (79), and hence resistance to fracture. Bone strength at the phalanges may not be as important as that measured at a usual skeletal fracture site, but a strong relationship between bone strength, elasticity and density of the distal radius with QUS measurement of the phalanges has been reported (37, 80). QUS performed in the tibia have also been found to demonstrate the mechanically anisotropic structure of bone, its modulus of elasticity, and bone strength (81, 82).

Ability of QUS to discriminate osteoporotic patients from controls

Most of the data reported in these sections are based on female studies although data exist on male osteoporosis (83-88).

Osteoporosis defined by DXA

Many studies demonstrated the utility of calcaneus QUS in the diagnosis of osteoporosis (57). Concerning our sites of interest, the analysis of some of these large databases has enabled the identification of appropriate diagnostic thresholds for osteoporosis, calculated on the basis of criteria selected by the WHO but which may differ from the classical absolute T-score value of -2.5 used in DXA. These values (20, 89-91) represent an important starting point for the use of such devices in screening of the postmenopausal female population. Apparently, from various studies, QUS seem to be an effective method in the identification of "DXA osteoporosis" (31, 32, 92). For screening osteoporosis in postmenopausal women, AD-SOS at the phalanges has a similar diagnostic sensitivity in the group of osteoporotic women over 50 years of age as DXA of the lumbar spine and femoral neck (25, 93). In 2004, Gambacciani et al. confirmed this potential. Performing a phalangeal QUS examination and a DXA scan on women, they used an AD-SOS T-score threshold equal to –2 (29). AD-SOS showed an Area Under the receiver operating Curve (AUC) of 0.72±0.02 in discriminating osteoporotic subjects from all other subjects at the lumbar spine, and an AUC of 0.71±0.02 in identifying osteoporotic and osteopenic subjects from normal subjects at the lumbar spine. In the same way, an AUC of 0.71±0.03 has been determined for AD-SOS in discriminating osteoporotic subjects from all the others at the femoral neck and an AUC of

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 (SXA) 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 0.68 to 0.89. Similarly, Damilakis et al. studying the discriminative ability of the SOS concerning fractures at the wrist, vertebrae, and ribs, found that the phalangeal SOS provided good discrimination (110). The OR was 1.47 for tibia, 1.69 for radius, and 2.69 for phalanx. The AUC ranged from 0.611 to 0.741. Nguyen et al. found that lower SOS at the distal radius, tibia, and phalanx were associated with increased risk of fracture in women (111). In a multivariate analysis, they determined that independent predictors of fracture risk were the distal radius SOS (OR per SD decrease = 1.8; 95% CI, 1.3-2.4), femoral neck BMD (OR per SD decrease = 1.9; 95% CI, 1.4-2.4), and age (OR per 5 years decrease = 1.2; 95% CI, 1.0-1.5). Data suggest that SOS at the distal radius was associated with fracture risk, independent of BMD and age.

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 BMI-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 0.740 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

by Guglielmi et al. with an age-adjusted standardized OR be 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). Knapp 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 (130-135), glucocorticoid excess (136, 137), lactose intolerance (138), rheumatoid arthritis (139-143), osteoarthritis (144), psoriatic arthritis (145), osteomalacia (146), hemodialysis (147-150), epilepsy (151, 152), osteogenesis imperfecta (153), Cushing's syndrome (139), bone medullary transplantation (154), calcium stone disease (155) and diabetes mellitus (156).

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 Study (OPUS), performed on more than 2,000 postmenopausal women, revealed that AD-SOS and UBPI measurements at the phalanges predict 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 frac-

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 osteotrophic therapies (166-170). A positive effect on bone due to treatment with Alendronate over a 12-month period was detected by QUS. The treatment group showed a significant increase in T-scores 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 amplitude 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 consensual 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 ade-

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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