Quantitative Ultrasound Techniques for the Assessment of Osteoporosis: Expert Agreement on Current Status

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ABSTRACT

Quantitative ultrasound (QUS) methods have been introduced in recent years for the assessment of skeletal status in osteoporosis. The performance of QUS techniques has been evaluated in a large number of studies. Reviewing existing knowledge, an international expert panel formulated the following consensus regarding the current status of this technology. To date, evidence supports the use of QUS techniques for the assessment of fracture risk in elderly women. This has been best established for water-based calcaneal QUS systems. Future studies should include the predictive validity of other QUS systems. Additional clinical applications of QUS, specifically the assessment of rates of change for monitoring disease progression or response to treatment, require further investigation. Its low cost and portability make QUS an attractive technology for assessing risk of fractures in larger populations than may be suitable or feasible for bone densitometry. Additional investigations that assess innovative QUS techniques in well defined research settings are important to determine and utilize the full potential of this technology for the benefit of early detection and monitoring of osteoporosis. (J Bone Miner Res 1997;12:1280–1288)

INTRODUCTION

OSTEOPOROSIS IS A SYSTEMIC skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture.(1) The disease represents a major world-wide public health problem.(2,3) Low bone density is an important determinant in the risk assessment of hip fractures, and recent studies have shown that a decrease in femoral bone density of one standard deviation increases the risk by a factor of two to three.(4,5) However, for a given bone density, the risk of hip fracture still increases with age, and there is an overlap of bone density between women with and without fractures.(4) This may be variously related to additional skeletal and extraskeletal factors. Extra skeletal factors include falls and the response to trauma. Skeletal factors in addition to bone mineral density (BMD) include accumulated fatigue and changes in trabecular or cortical architecture.

In the last 25 years, several noninvasive techniques based on the attenuation of ionizing radiation have been developed to quantify BMD in the axial and peripheral skeleton. These include single photon absorptiometry (SPA), single X-ray absorptiometry (SXA), dual X-ray absorptiometry (DXA), and quantitative computed tomography (QCT).(6) They represent valid methods for the determination of BMD and explain about 60–80% of the variation in bone strength.(7,8) However, they provide only limited information on bone structure and bone material properties. Consequently, researchers and clinicians are looking for new methods that may have a role in assessing skeletal status. An ideal screening tool should be inexpensive, the patient should be exposed to little if any risk or discomfort, and it should detect fragility, whatever its basis, and not just decreased BMD. It is possible that a combination of elasticity, structure, and density information will provide a more sensitive indicator of fracture risk than techniques that reflect bone density alone.

Quantitative ultrasound (QUS) methods have been developed and introduced in recent years for the assessment of skeletal status.(9–12) Researchers investigating osteoporosis by means of QUS have reported favorable results, and most recently, manufacturers have released a great variety of commercial devices for QUS assessment at peripheral
measurement sites.\textsuperscript{(13–18)} Appreciating the substantial potential of this new technology but recognizing the limited experience that has been gathered during this relatively short time period,\textsuperscript{(19)} both researchers and clinicians have expressed the need for a consensus statement on ultrasound applications in osteoporosis. The goals of this statement are to review existing knowledge and to aid and guide further development and clinical introduction of QUS technologies. An international expert panel with members from Asia, Australia, Europe, and North and South America held two meetings, one in Amsterdam, The Netherlands, on May 21, 1996 and another in Seattle, WA, U.S.A., on September 10, 1996 and formulated the following consensus. It has been endorsed by several major international osteoporosis societies.\textsuperscript{1}

\textbf{THE POTENTIAL}

The investigation of QUS techniques for noninvasive evaluation of skeletal status is promising for the following reasons:

1. Ultrasound is a mechanical wave. When passing through bone it causes both the cortex and the trabecular network to vibrate on a microscale. The laws of physics describe the relationship between mechanical properties (in this case of bone), three-dimensional bone architecture, and velocity or attenuation of transmitted ultrasonic waves. An assessment of QUS parameters should allow one to deduce mechanical properties of cortical and trabecular bone which in turn are important determinants of whole bone stiffness, failure load, and fracture risk.\textsuperscript{(20–24)}

2. Ultrasound has been successfully employed for many years for nondestructive material testing.\textsuperscript{(25)} Both scattering characteristics and ultrasound velocity changes have been used to evaluate mechanical competence and detect the presence of damage in both materials and structures. Nevertheless, the applicability of this technology to the requirements of medicine and specifically for fracture risk prediction has to be validated independently.

3. Bone has a mechanically anisotropic structure. In contrast to bone density measurements, which are based on X-ray attenuation, ultrasound parameters reflect the structural anisotropy of bone.\textsuperscript{(26–28)} Therefore, QUS may have greater potential to be developed into a tool for the comprehensive noninvasive assessment of threedimensional structure and strength.\textsuperscript{(29,30)} However, this would most likely require ultrasonic assessment in several directions and, perhaps, at different frequencies and with differing beam profile which may not be feasible at relevant measurement sites.
4. Ultrasound assessment can be performed noninvasively and the patient is not exposed to ionizing radiation. This enhances the patient’s acceptance of the test.

5. Ultrasound technology is less expensive than X-ray technology and devices can be designed to be portable. Therefore, ultrasound has a potential for wider applicability compared with conventional X-ray–based bone densitometry.

6. The lack of ionizing radiation facilitates placement, licensing, and operation of equipment because of less demanding regulations for personnel and space. Still, appropriate training of personnel and sufficient quality assurance measures need to be ensured.

One can foresee that ultrasound techniques may have the potential for preventive screening for osteoporosis as well as monitoring therapeutic interventions.

ACHIEVEMENTS TO DATE

Following the proposal by Langton et al. in 1984 to study broadband ultrasound attenuation (BUA) for the assessment of osteoporosis and a number of years with slow but steady progress, the number of QUS studies has dramatically increased in the past few years. For example, close to 100 QUS studies were presented at the World Congress on Osteoporosis in Amsterdam in May 1996, demonstrating the enormous academic interest in this development. Without major exceptions, these and previous studies yielded encouraging and exciting results. They can be summarized as follows:

1. A significant association between QUS results and the prevalence of osteoporotic fractures was observed. Fracture risk discrimination by means of QUS was about as strong as for absorptiometric techniques such as SXA and DXA.

2. Two independent prospective studies with sample sizes of 6500 to 10,000 women showed that QUS results (as measured at the calcaneus) can be used to predict future fracture risk in older women. Two QUS parameters were shown to perform equally well: BUA, which reflects the frequency dependence of ultrasound attenuation, and speed of sound (SOS). Results from these studies demonstrating the increase in fracture risk with decreasing QUS results are shown in Figs. 1 and 2. The gradients of risk reported for QUS were similar to those for DXA.

3. Both of the aforementioned studies also reported that QUS parameters predicted hip fractures independently of BMD. However, this does not necessarily imply that fracture risk prediction could be improved by a combined assessment of QUS and bone density. This issue is still controversial and further studies are needed to determine whether such improvements can be achieved.

4. Cross-sectional studies on age-related changes of QUS parameters demonstrated substantial decreases during the period immediately following the menopause but also in very elderly subjects. The changes seen were comparable to those observed using conventional X-ray–based bone densitometry.

5. The reproducibility of QUS measurements has been investigated in several studies. Precision of BUA and SOS has not yet matched that of bone densitometry techniques. Combinations of BUA and SOS may improve precision.

6. Studies in human cadavers and human or bovine bone specimens have demonstrated that QUS measurements are associated with the material properties of trabecular bone, as well as with the failure load of the proximal femur.

7. Studies on bone specimens and for carefully site-matched measurements in vivo showed that QUS and bone densitometry results are highly correlated as long as they are measured along a single direction and at the same location. However, if an examination is carried out in three mutually perpendicular directions, ultrasound—unlike X-ray–based bone densitometry—demonstrates substantial differences depending on the direction of propagation. This dependency parallels the anisotropic structure of bone, its modulus of elasticity, and bone strength.
FIG. 2. Incidence of fractures of any type except spine fractures as predicted prospectively from QUS (BUA) of the calcaneus, and BMDcal and BMDfn; expressed as relative risk ratios per standard deviation change with 95% confidence intervals. (Adapted with permission from the SOF study.\(^{(42)}\))

8. Using currently commercially marketed equipment, the correlation of calcaneal QUS measurements and calcaneal BMD measurement is moderately high \((r = 0.6–0.8)\)\(^{(55,56)}\); correlations between QUS measurements and BMD of the spine or the proximal femur is modest \((r < 0.5)\)\(^{(60–62)}\). Therefore, QUS results cannot be used to predict BMD of the main fracture sites.\(^{(60–62)}\)

CHALLENGES

The achievements of the past years are numerous and impressive, but in specific areas further research and longer practical experience are needed. The following topics merit specific attention.

1. *Diversity:* The commercial QUS devices introduced show a greater technological diversity than bone densitometry equipment. This may reflect a strength of QUS but it also represents a challenge for the validation process. Results obtained on a validated device cannot necessarily be directly translated into performance statements of other technologically different QUS devices. The following groups of approaches and equipment have been developed into commercially available systems:

   A. Calcaneal fixed single point transmission systems employing either water-based foot placement\(^{(41,42)}\) or coupling by means of ultrasonic gels.\(^{(63)}\)
   B. Calcaneal imaging devices allowing for flexible placement of regions of interest within the calcaneus.\(^{(57,64)}\)
   C. Single point QUS systems for measurements at the finger phalanges using gel coupling.\(^{(65–70)}\)
   D. Assessment of ultrasound velocity measurements of the tibial cortex using gel coupling.\(^{(45,71–73)}\)

   In addition, a number of other ultrasound approaches including devices for measurements at the patella\(^{(60,74–76)}\) or ulna (using a reflection technique)\(^{(77,78)}\) have been described. In one study, ultrasound transmission velocity measured at the patella was significantly associated with incidence of vertebral fractures.\(^{(74)}\) However, devices for measurements at the patella or ulna are not currently commercially marketed. Ultrasonic assessment of the skin as a different means for assessing osteoporosis has been proposed. However, this is a fundamentally different approach that is not covered by the scope of this publication. This document is limited to an assessment of devices of categories A to D recognizing that there may be future technological developments beyond the current status. Among the devices of categories A to D, fracture risk prediction to date has only been shown prospectively for water-based calcaneal QUS systems.

   In addition to diversity in the technology there are also differences in the definition of QUS parameters among manufacturers.\(^{(79)}\) Moreover, SOS as measured in commercial devices is based on transit velocity that is partially (and in a device-specific fashion) affected by attenuation. These sources of added diversity need to be acknowledged.

   2. *Normative data:* Reference data for commercial devices are limited to date.

   3. *Studies in men and younger women:* Fracture risk prediction based on QUS also needs to be investigated in men and early postmenopausal women.

   4. *Quality assurance:* To date, there is only limited experience with quality assurance approaches for QUS devices. This deficiency affects the credibility of this approach. The influence of operator impact and other error sources also need to be studied. A comprehensive quality assurance concept should address issues such as QUS reference phantoms for stability measurements and assessment of accuracy, certification of personnel and equipment, and standardized scanning and analysis procedures specifically tailored to osteoporosis assessment by means of QUS.

   5. *Standardization:* QUS devices employ diverse technology and different methods for calibration. Clinical use would benefit from standardized methods of calibration and expression of measurement results. These methods need to reflect the complex nature of ultrasound interaction with bone. The “International Committee for Standards in Bone Measurement” is currently addressing these issues extending previous work on bone densitometry.\(^{(60)}\)

   6. *Precision and sensitivity:* Many authors have investigated the short-term precision of QUS measurements.\(^{(37,38,45,46,48,62,73,81)}\) However, there is little information about the long-term precision in vivo, and only a few longitudinal studies on changes of QUS parameters over time have been published.\(^{(32,82,83)}\) While precision expressed as percentage looks excellent for some QUS parameters,\(^{(45,73,81)}\) this may be misleading if responsiveness to skeletal changes is low.\(^{(48,62,73)}\) Responsiveness is affected both by the measurement technique and the measurement site. To assess the sensitivity to monitor changes, the ratio of precision and responsiveness is important. This ratio can be expressed as standardized precision error and in most studies—with some recent exceptions\(^{(32,38)}\)—it has appeared to be higher compared with standard bone densitometry approaches. This
would limit the ability of QUS to monitor skeletal changes in individual subjects. It remains to be seen whether the newer devices (e.g., imaging systems) or parameters based on combinations of BUA and SOS have improved precision.

7. Accuracy: Accuracy in the sense of an unbiased assessment of skeletal properties is important for diagnostic applications of QUS. For bone densitometry techniques, accuracy is typically described as the ability to provide an unbiased assessment of bone mineral content. Since calcium represents the dominant factor affecting X-ray absorption, these techniques have proved to provide an assessment of calcium content with accuracy errors ranging around 5–15%.\(^{(84)}\) Ultrasound propagation in bone is extremely complex\(^{(21)}\) and ultrasonic attenuation and velocity are affected not only by mineral content but also by other material and structural properties. Therefore, accuracy should be expressed with regards to these properties. The most appropriate but also most ambitious parameter would be the accuracy of assessing breaking strength of the bone. However, this parameter is difficult to measure, depends on the type of impacting force, and is directionally anisotropic. Therefore, evaluation of accuracy errors for the assessment of surrogate measures, such as BMD or elasticity along the path of ultrasound transmission, may be useful.

The identification and investigation of accuracy error sources is of substantial importance. Accuracy as well as precision is decreased by anatomically inconsistent placement of the measurement region.\(^{(85,86)}\) Careful positioning of the patient is critical and flexible placement of the region of interest (e.g., by imaging techniques) may improve accuracy.\(^{(64,85,86)}\) This issue becomes of even greater importance as more diverse populations (e.g., including men or children) are studied.\(^{(87)}\) Diffraction affects both attenuation and velocity measurements\(^{(88,89)}\) and represents a device-specific error source. Variability of bone width, soft tissue thickness or composition, marrow composition, and temperature represent patient-dependent components of accuracy errors.\(^{(79,86,90–92)}\) Their magnitude can be investigated independently of an agreement on the definition of accuracy. Ideally, investigations should be carried out in situ. However, use of appropriate bone-like phantoms can also be helpful. All of these aspects should be investigated in comparative studies contrasting the performances of different ultrasonic with those of densitometric approaches.

RECOMMENDATIONS FOR CLINICAL APPLICATION OF QUS

Three areas for potential clinical use of QUS devices can be named: diagnosis of osteoporosis, fracture risk assessment, and monitoring of skeletal changes (due to treatment or progression of disease).

Diagnosis of osteoporosis

Both cross-sectional and prospective studies have demonstrated close associations between QUS parameters and osteoporotic status. However, due to the ambiguities in assessing accuracy of QUS and the moderate correlation of densitometric and ultrasonic results, currently there is no agreement on how results of QUS devices should be interpreted in order to diagnose osteoporosis. In the future, it may be possible to devise criteria similar to those used for bone densitometry (staging osteoporosis status based on T scores as proposed by a (WHO) study group.\(^{(93)}\) However, currently there is no consensus on this issue. A parallel assessment with a standard bone densitometry approach is recommended.

Fracture risk prediction

For water-based calcaneal QUS systems, it has been shown in two independent prospective studies that QUS parameters including BUA\(^{(41,42)}\) and SOS\(^{(41)}\) can be used to predict the risk of osteoporotic fractures in elderly women. The performance of these devices equaled that of the best DXA approaches. For specific prediction of hip fracture risk, QUS devices showed stronger performance than for other fractures. However, one of the two prospective studies reported an even better performance for DXA measurements of the femoral neck.\(^{(42)}\) Clinical use of these QUS devices hinges upon availability of adequate normative databases and implementation of rigid quality assurance procedures. For all other QUS devices, currently only cross-sectional studies comparing osteoporotic and normal individuals are available. Results generally demonstrated comparable performance for devices of categories A to D listed above. Those two devices of category A for which both cross-sectional as well as prospective study results are available demonstrated comparable performance independent of the study design. Therefore, the prospects for confirmation of cross-sectional results in prospective fashion are good. However, prior to recommending any other QUS device for fracture risk assessment, prospective validation is important. These studies are in progress.

Monitoring skeletal changes

Because of the limited experience, monitoring of skeletal changes solely by means of QUS cannot be recommended yet. The time periods to follow individual subjects would most likely exceed those required for bone densitometry. This would probably result in follow-up time periods of several years, a timeframe that is inappropriately long, particularly in view of the rapid technological development in QUS technology. 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.

In summary, it has been shown that water-based calcu-
neal QUS systems can be used for fracture risk prediction in elderly women. All other clinical QUS evaluations, particularly if the results are below the normal range, should presently be complemented by bone densitometry, which should also be used for follow-up. Whether subjects with normal or above normal QUS results could be exempted from further DXA examination or obtain their DXA examination some time later or which other strategies appear to be appropriate should be evaluated further, both with regard to medical and cost effectiveness aspects. If proven effective, this may offer primary care physicians or physicians with limited access to bone densitometry the possibility to select the high-risk patients who would subsequently be referred to a center where densitometry is available. Once validated, QUS systems could also be employed at sites where X-ray-based technology is contraindicated.

RESEARCH PERSPECTIVES

Intensive multifaceted research is currently ongoing in many different areas of applications of QUS techniques. Several areas, however, appear to be of particular importance because they either address current deficits in knowledge about QUS, deficiencies of bone densitometry, or they represent particularly promising future applications of QUS.

Studies in vitro

Experimental studies should be carried out in vitro to improve the understanding of the underlying mechanism of QUS approaches, to study the limitation of current QUS approaches, and to investigate innovative QUS techniques. Investigations should specifically address the following issues:

1. Assessment of associations between QUS, BMD, bone structure, and material properties of bone tissue in order to separate these relationships and provide deeper knowledge about what is measured by QUS parameters such as BUA and SOS.
2. Relationships between QUS and mechanical properties both of the bone measured by QUS as well as of bone at fracture sites (i.e., the proximal femur and vertebral bodies). Since these studies are highly dependent on the subject group investigated, parallel investigations using QUS and standard bone densitometry approaches should be carried out for comparative assessments.
3. The impact of the degree of bone mineralization (as opposed to the amount of bone tissue), its anisotropy, crystalline and collagenous structure, and mechanical properties as they relate to QUS parameters.
4. Testing different QUS techniques. The measurement of BUA and SOS as achieved with current devices represents a narrow range of the entire potential for ultrasound measurements. There are numerous other methods that may be tested, such as more extensive characterization of the attenuation function, true frequency-dependent velocity estimates, scattering methods, and other derived ultrasound parameters. These methods should be investigated over a broader range of frequencies.
5. Assessment of error sources. Compared with X-rays, the interaction of ultrasound in bone and soft tissue is substantially more complex. Investigations should be initiated with the aim of providing directions for improvements in technology. All of these studies need to be carried out with particular attention to changes in excised tissue. They may substantially affect ultrasound results particularly if soft tissue is included.

Studies in vivo

The performance of current QUS devices should be studied further in vivo. In addition, developing improved methods for fracture risk prediction beyond the current limits of bone densitometry would be of value. Therefore, innovative QUS approaches and strategies for combined use of QUS and bone densitometry should be investigated in well-defined and controlled research protocols. The following issues should be addressed:

1. Prospective fracture studies as the gold standard for validation of QUS application in a clinical setting. The studies should include newer types of QUS devices, measure women and men at extended age ranges, and include non-white populations.
2. Regional and ethnospecific normative databases should be compiled and validated independently for each type of equipment.
3. The use of QUS in peri- and early postmenopausal women to determine who might most benefit from preventive measures.
4. QUS status in secondary osteoporosis.
5. The impact of treatment effects on QUS parameters.
6. Longitudinal studies monitoring disease progression in various forms of primary and secondary osteoporosis. Assessment as to whether changes in QUS parameters in longitudinal studies predict changes in fracture risk. Parallel measures of bone densitometry should be incorporated in order to investigate differential changes in ultrasonic versus densitometric parameters.
7. Longitudinal studies on the effect of treatment modalities with parallel densitometric evaluations.
8. Comparison of the performance of different QUS parameters and their combinations.
9. The use of QUS in children, e.g., for diagnosis and monitoring of disorders of the developing skeleton.
10. Assessment of error sources impacting on accuracy and precision.
11. Investigation of innovative QUS approaches, e.g., other frequency ranges, additional parameters, or combinations of several QUS parameters observed in vitro can be exploited clinically. Evaluation of the performance of QUS imaging systems (spatial resolution, precision, accuracy) and their image analysis software (optimum location and size of region of interest, operator impact).
Other studies

1. Defining quality assurance measures that result in codes for good practice for QUS. Optimal concepts for quality assurance need to be devised and tested. Specifically, to develop QUS reference phantoms that mimic bone with regards to both velocity and attenuation (and specifically the frequency dependency of attenuation) and that can be used for assessment of precision and accuracy. Phantom designs should reflect the shape and composition of the bone investigated by the specific QUS device. The phantoms should be easy to use and allow highly reproducible and quick measurements that can be performed on a daily basis.

2. Standardizing QUS measurements. A listing of clear, measurable definitions of QUS parameters including BUA, SOS, and combinations should be compiled. Standardized methods for calibration and expression of measurement results paralleling those specified for DXA should be devised.

3. Concepts for cost effective use of QUS. Guidelines for appropriate use of QUS should be developed and modeled to provide perspectives for clinical introduction of QUS approaches.

4. Theoretical advances to improve the understanding of fundamental principles governing the ability to distinguish osteoporotic from healthy bone. Analytical and computational studies of ultrasound propagation in bone should be carried out addressing issues like diffraction, dispersion, etc. in the context of current QUS technology.

CONCLUSION

A substantial body of knowledge regarding the performance of QUS techniques has been gathered. To date, evidence supports the use of QUS techniques for the assessment of fracture risk in elderly women. This capability has been best established for water based calcaneal QUS systems.\(^{41,42}\) Future studies should include the predictive validity of other QUS systems. Additional clinical applications of QUS, specifically the assessment of rates of change for monitoring disease progression or response to treatment, require further investigation. Its low cost and portability makes QUS an attractive technology for assessing risk of fractures in larger populations than may be suitable or feasible for bone densitometry. Additional investigations that assess innovative QUS techniques in well defined research settings are important to determine and utilize the full potential of this technology for the benefit of early detection and monitoring of osteoporosis.

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