Ultrasound of the Skeleton: Review of Its Clinical Applications and Pitfalls

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Quantitative ultrasound (QUS) is receiving considerable attention in the assessment of osteoporosis because of its ease of use, lack of radiation exposure, region of interest, and relatively low costs. These features have made the technique appealing for screening adult and pediatric patients. This article discusses some of the clinical applications, limitations, and strengths of QUS.

Introduction

In addition to primary osteoporosis, quantitative ultrasound (QUS) has been studied in several diseases that may affect the skeleton, *ie*, the effects of inflammatory bowel disease on the skeleton [1–3]. Disparate conclusions are reached as to its suitability for screening purposes in large part because of its lack of sensitivity compared with standard dual energy x-ray absorptiometry (DEXA) of the spine and hip. Approximately 66% to 72% of patients with osteoporosis are identified by DEXA. Patients with renal osteodystrophy have a significant correlation between QUS and hip DEXA ($r = 0.68–0.79$, $P < 0.001$) and excellent sensitivity and specificity; however, the positive predictive value is poor [4,5]. A novel use of QUS in evaluating patients with various disorders of collagen metabolism shows differences in measurements that suggest an inherent difference in the abnormalities of collagen in each disease [6,7]. Patients with hyperparathyroidism have differences in QUS values as a function of the cortical and cancellous proportions in different anatomic sites, much like that found in DEXA [8]. There is evidence that QUS tracks the changes in skeletal repair after surgical correction of the disease [9]. Hyperthyroid patients have depressed QUS parameters as part of the active disease [10]. With this wealth of potential utility, why are there concerns and confusion about this method?

Clinical Applications and Pitfalls

Similar to ultrasound in other systems, bone ultrasound relies on a transducer to emit sound waves. These waves travel through tissue to a receiving transducer, which then analyzes certain characteristics of the incoming waves. However, in QUS of bone, the emitting and receiving transducers are two separate systems, each placed on opposite sides of the tissue. Generally, the heel has been chosen because it is an easily accessible, weight-bearing bone with high trabecular content. A heated water bath or gel couples the systems to the skin to diminish loss of the ultrasound waves.

Two characteristics of the transmitted waves form the basis of QUS: speed of sound and attenuation. Speed of sound refers to the distance traveled per unit time and is reported as meters per second. The homogeneity of healthy bone promotes sound transmission, whereas the heterogeneity of trabecular-poor osteoporotic bone decreases sound transmission. Thus, the speed of sound transmission is higher in healthy bone and lower in osteoporotic bone. Depending on the type of QUS machine used, speed of sound may be reported as limb velocity, bone velocity, or time of flight.

The second wave characteristic measured in QUC is attenuation. Attenuation is defined as energy loss occurring as an ultrasound beam traverses a medium. Healthy trabecular bone is a highly attenuating medium because it scatters sound waves. To traverse bone tissue, lower frequency sound waves must be used because attenuation is linearly proportional to frequency. QUS of bone uses sound wave frequencies of 0.2 to 1.0 MHz, significantly less than that used for abdominal or vascular ultrasound. Waves are transmitted at multiple frequencies throughout this low range and the attenuation quantified. The slope of attenuation as a function of frequency is known as broadband ultrasound attenuation (BUA) and is reported as decibels per megahertz. Compared with healthy bone, osteoporotic bone is less attenuating and BUA values lower.

In many systems, the characteristics of SOS and BUA are combined to give a single measure. The Lunar Achilles system reports the stiffness index [11], whereas Hologic Sahara reports the quantitative ultrasound index. It is claimed that these indices improve coefficients of variation

and, therefore, precision. These measures are then compared with reference ranges and reported as T scores.

What features of bone are measured by QUS? Many authors have reported significant but moderate correlation coefficients with bone mineral density of 0.4 to 0.7 [11,12,13••]. The correlation coefficients have been similar regardless of site or method used to measure BMD. These data have led several authors to suggest that QUS may measure qualities of bone architecture other than density [14••,15,16]. Bone architecture refers to the three-dimensional arrangement of trabeculae and includes porosity, connectivity, and orientation of the trabecular plates. This issue remains controversial.

Prediction of fracture risk has been the basis of ultrasound's acceptance as a screening tool for osteoporosis. Three major prospective studies have concluded that QUS is able to predict hip fracture. Porter *et al.* [17] studied more than 1400 institutionalized elderly women and found that BUA was related to fracture incidence when combined with other factors such as mentation and mobility. Subsequently, the Epidemiologie de l'Osteoporose (EPIDOS) study, involving more than 5600 French women 75 years of age and older, found that the relative risk of hip fracture for a 1 SD reduction in BUA and SOS was similar to that for DEXA of the hip [18••]. Baur *et al.* [19] showed similar results in a cohort of more than 6000 women (mean age 65 years) observed for a mean of 2 years. Again, the relative risk of hip and other nonspine fractures for each SD reduction in BUA and SOS was similar to that of DEXA [19].

Multiple studies have addressed the diagnostic accuracy, sensitivity, and specificity of QUS [20,21,22•,23]. The results are not always consistent because the studies used different manufacturer's machines and, more importantly, different definitions of osteoporosis. It seems unlikely that the World Health Organization's (WHO) definition of osteoporosis (*ie*, DEXA T score < -2.5 SD) can be applied to QUS. Goldstein *et al.* [24] evaluated 319 postmenopausal women using hip DEXA and the Hologic Sahara ultrasound system. Following WHO guidelines, subjects were classified into groups of normal, osteopenic, or osteoporotic based on femoral neck DEXA T score and their QUS T score. Classification results for various Sahara thresholds were compared with those of DEXA, and optimal agreement was found for Sahara thresholds between T score -1 and T score 0. A sensitivity of 82% (for identifying patients osteoporotic by DEXA) was obtained for a Sahara T score -1. False-positive and false-negative rates were 10% and 6%, respectively [24].

Ingle *et al.* [25] recently reported a study of 329 women from the ages of 20 to 80 years using four different QUS systems (Lunar Achilles, Hologic Sahara, CUBA Clinical, and DMB sonic finger QUS). SOS T scores varied between machines (-1.4 to -2.9) and from BUA scores (-1.1 to -2.3). When SOS and BUA were combined and expressed as one parameter to better discriminate osteoporotic patients, the T scores were -1.3 SD for the Hologic Sahara quantitative ultrasound index and -2.4 SD for the Lunar Achilles stiffness index, respectively [25]. These differences suggest that the WHO criteria for osteoporosis cannot be applied universally to QUS. However, using a new system (QUS-2), Chen *et al.* [26] reported similar T scores for hip DEXA and heel BUA, but not spine DEXA, in a study of 104 white women ages 25 to 84 years.

There are several confounding variables that influence the measurements of QUS, which include genetics, race, activity, and positioning/region of interest. A recent study of black women, Asian-American women, and white men showed marked differences in ultrasonography measurements between the groups of women of age 25 to 75 years and between the male and female groups [27]. It is well-known that premenopausal daughters of mothers with established osteoporosis have lower DEXA scores in the spine and hip than the same measurements in daughters of mothers without osteoporosis. Ultrasound does not identify such a difference [28]. However, in a study evaluating measurements in monozygotic and dizygotic twins, ultrasound data were better correlated in monozygotic twins than in dizygotic twins. Environmental influences had no effect [29]. Ethnic differences suggest that normative databases must be specific to the population under study. In a study of German women, age 50.5 ± 11.5 years, a decline in speed of sound, attenuation, and the calculated stiffness index was found throughout the ages tested. More interesting was that the German population had significantly higher measurements compared with their American-based cohorts [20]. In addition, weight influences the measurement. Ultrasonography of the calcaneus proved to be better correlated after correction for body weight in a group of elderly patients 65 to 87 years of age [31].

Activity level has a negative influence on measurements. In a group of young subjects, ages 21 to 35 years, calcaneal ultrasound was checked before and after a publicly sponsored "walk for osteoporosis." After a leisurely 1- to 2-mile walk around a college sports track, there was a significant decline in the T score, which reversed to normal after a period of rest [32]. Hence, activity before a measurement may cause false-positive results.

The region of interest being measured contributes to intertest and intratest variability. Not all manufactured products use the same method to define the region of interest [33]. In addition, positioning errors of the foot account for most of the intratest variability. These inconsistencies make repetitive prospective measurements in the same patient inaccurate. In a 2-year prospective study, speed of sound, attenuation, and stiffness index changed 27%, 19%, and 11%, respectively. This finding implied that, to detect a significant biologic difference in the same person, changes had to be at least twofold greater [34••]. Several studies address methods to improve reproducibility. One study defines a region of interest

using the posterior tuberosity of the calcaneus as a landmark [35]. Another defines region of interest as the area in the calcaneus with the minimum attenuation [36••]. This approach has a 1.2% coefficient of variation compared with 3.8% with the fixed positioning. Another study showed impressive precision by calculations involving the size and shape of the entire calcaneus [37••]. Furthermore, right- and left-sidedness influence results, at least in patients with unilateral hip arthroplasties [38].

Other anatomic sites are being investigated to help eliminate this problem of imprecision. The major areas of study are ultrasound of the tibia and the distal phalanges of the hand. These studies show a significant correlation with DEXA of the spine and hip and predict risk of fracture [39–41]. In general, these studies are in an early investigative stage and require further work on longitudinal precision, anatomic correlation, and region of interest.

Conclusions

Skeletal ultrasound, which is being studied extensively, is a useful technique because of its low cost of investment, ease of use, and lack of radiation exposure. Despite US Food and Drug Administration approval, it has limitations, as does any technique. Applicability of the WHO criteria for osteoporosis needs to be clarified and a definition of osteoporosis using QUS parameters established. Imprecision with repetitive measurements is the biggest drawback. The longitudinal imprecision makes this instrument best used to screen patients for further evaluation with DEXA measurements, which remain the gold standard.

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