Alberta Heritage Foundation for Medical Research

Quantitative ultrasound for bone density measurement

Joanne Homik and David Hailey

September 1998

HTA 11

Quantitative ultrasound for bone density measurement

Joanne Homik and David Hailey

September 1998

This Health Technology Assessment Report has been prepared on the basis of available information of which the Foundation is aware from public literature and expert opinion, and attempts to be current to the date of publication. It has been externally reviewed. Additional information and comments relative to the Report are welcome, and should be sent to:

Director, Health Technology Assessment
Alberta Heritage Foundation for Medical Research
3125 ManuLife Place, 10180 - 101 Street
Edmonton
Alberta T5J 3S4
CANADA

Tel: 403-423-5727, Fax: 403-429-3509

ISBN 1-896956-11-4

Alberta's health technology assessment program has been established under the Health Research Collaboration Agreement between the Alberta Heritage Foundation for Medical Research and the Alberta Health Ministry.

Acknowledgments

The Alberta Heritage Foundation for Medical Research is most grateful to the following persons for their comments on the draft report and for provision of information. The views expressed in the final report are those of the Foundation.

Dr. David Hanley, Faculty of Medicine, University of Calgary

Dr. Brian Lentle, Vancouver Hospital

Dr. Devidas Menon, Institute of Pharmaco-Economics, Edmonton

Dr. Kerry Siminoski, Endocrine Centre of Edmonton

Ms. Brenda Waye, Alberta Health, Edmonton

Contents

Summary

- There is increased interest in the use of quantitative ultrasound (QUS) for diagnosis of osteoporosis.
- Ultrasound devices for diagnosis of osteoporosis measure the speed of sound (SOS) and/or broadband ultrasound attenuation (BUA) at the calcaneus. Both wet systems, which make use of a water bath in which the foot is submerged, and dry systems, in which the heel is in direct contact with the ultrasound transducers, have been produced.
- Data could be identified for five individual machines which are possibly relevant to the Canadian market. Comparative data on these devices are limited, though all appear to have about the same level of precision. Coefficients of variation for BUA seem somewhat higher than those for dual energy x-ray absorptiometry (DXA) while those for SOS are somewhat lower.
- There are no data available on accuracy. The concept of accuracy for the technology is unclear as the attribute being measured is not well defined.
- Both BUA and SOS measurements show only moderate correlation with those from DXA.
- Results from most studies indicate good correlation of ultrasound parameters with fracture prevalence for study populations. Values for relative risk are similar, though somewhat lower than, corresponding data for DXA measurement.
- Some evidence suggests that DXA and QUS are measuring different physical phenomena and may identify different groups of people as being at risk for fracture. However, there is no evidence of increased capture of an at-risk population if both tests are performed.
- There is very little information available on the use of QUS outside the research setting. Measures of its performance and guidelines for use in routine clinical practice are not yet available.
- There is no evidence that use of the technology appropriately influences management decisions or improves health outcomes. From the available information, it is suggested that use of QUS as a pre-screening tool prior to DXA would not be appropriate.

- QUS may provide an option for use in under-serviced populations as an alternative to DXA. However, if such an approach were adopted, a number of practical issues would need consideration, including the need for confirmatory tests and potential duplication of services.
- At this stage, quantitative calcaneal ultrasound appears to a be promising diagnostic technology but its role in diagnosis of osteoporosis remains unclear. Further evidence regarding its long-term precision, predictive ability and potential cost-effectiveness is required before its place in routine health care services can be established.

Glossary

AUC	area under the curve (receiver operating characteristic curve)
BDM	bone density measurement
BMD	bone mineral density
BUA	broadband ultrasound attenuation
CV	coefficient of variation
dB	decibels
DPA	dual photon absorptiometry
DXA	dual energy x-ray absorptiometry
HRT	hormone replacement therapy
MHz	megahertz
OR	odds ratio
QCT	quantitative computed tomography
QUI	quantitative ultrasound index
QUS	quantitative ultrasound
ROC	receiver operating characteristic
RR	relative risk
sCV	standardized coefficient of variation
SI	stiffness index calculated from the SOS and BUA
SOS	speed of sound
SXA	single energy x-ray absorptiometry
T score	standardized BMD as compared to sex-matched young adults
Z score	standardized BMD as compared to age and sex-matched individuals

Introduction

This report has been prepared in view of the increasing interest in ultrasound technology for diagnosis of osteoporosis. Until recently, quantitative ultrasound (QUS) was mainly being used in research settings. This procedure is still not covered by provincial fee schedules. The recent FDA pre-marketing approvals of the Hologic Sahara and Lunar Achilles devices for general use in the diagnosis of osteoporosis can be expected to increase interest in the use of this technology by both consumers and healthcare providers.

The issues addressed in this report include the current status of quantitative ultrasound technology, its performance and predictive value compared to x-ray based technologies, availability of machines, and issues related to its use in Canada. Details of methodology used for the literature review are given in Appendix A.

Osteoporosis implies a decrease in bone mass and an increased risk of fractures. With osteoporotic fractures come increased pain and disability, and even death. Those at increased risk are post-menopausal women, elderly individuals of both sexes, and people on medications, such as corticosteroids and heparin, that deplete bone. The purpose of testing with bone density measurement is to identify those with low bone mass and treat them with drugs that halt or reverse the loss of bone, in an effort to avoid the occurrence of a fracture. It is hoped that knowledge of bone mass will allow identification of those individuals at highest risk of fracture and have an impact on decisions affecting their management. Osteoporosis affects thousands of Albertans, with a substantial proportion of those going on to fracture.

Diagnosis of osteoporosis and fracture prediction are most commonly accomplished by radioisotope or x-ray based techniques including single photon absorptiometry (SPA), dual photon absorptiometry (DPA), quantitative computed tomography (QCT) and dual energy x-ray absorptiometry (DXA). These devices measure bone mineral density (BMD), an indicator of bone mass.

DXA is currently the most widespread diagnostic technique used in the diagnosis of osteoporosis. The limitations of DXA are its relative expense and known performance limitations (76). Also, DXA may not be readily available to those in smaller communities. QUS, on the other hand, is being marketed as an office procedure due to the small size and lower cost of US machines, as compared with DXA. The potential attractions of ultrasound include a less expensive procedure and better access for patients. These are tempered by the reports of performance limitations. Ultrasound also avoids use of ionizing radiation, although this is of

limited significance as a DXA measurement provides considerably less radiation exposure than a chest x-ray.

There is mixed opinion regarding the proposed role for QUS, with some suggesting it could replace DXA or other x-ray based diagnostic techniques where they are not available. The performance of QUS needs to be evaluated before its use becomes widespread. A major limitation for the technology at present is the lack of a phantom for cross-calibration and standardization (Lentle, personal communication).

Description of the technology

Quantitative ultrasound measures speed of sound (SOS) and broadband ultrasound attenuation (BUA). The most commonly used site is the heel (calcaneus), though measurement at other sites such as the tibia and phalanges has also been studied. The units may make use of a water bath, in which the foot is submerged, or else a dry system where the heel is in direct contact with two ultrasound transducers. It is important for there to be good acoustical contact between the skin and the transducer. A coupling gel or pads are used to facilitate contact. One of the ultrasound transducers emits an ultrasound wave. On its passage through the heel, both the speed and amplitude of the wave are changed. These changes are detected by the second transducer.

The differences in velocity and amplitude are recorded as speed of sound and attenuation measurements respectively. The Lunar Achilles machine calculates a quantity referred to as a stiffness index (SI) from the SOS and BUA values (this appears to have no direct relationship to the term "stiffness" used in materials science). The Hologic Sahara device reports a quantitative ultrasound index (QUI), calculated from SOS and BUA. It is unclear whether SI and QUI are calculated in the same manner.

What measurements are made with quantitative ultrasound?

Velocity may be measured as limb velocity (bone and soft tissue of the heel), bone velocity, and time of flight (TOF) (difference in speed through water versus through water with a heel in it). Water bath methods use TOF and assume a fixed heel width. This gives the greatest precision but the smallest dynamic range (range of normal values). Contact systems use the limb velocity. Velocity can be related algebraically to the elastic modulus of bone, a measure of bone's deformability. Velocity has been correlated with the mechanical strength of the calcaneus (7).

Attenuation describes the loss of wave energy as an ultrasound signal passes through bone, mainly through absorption and scattering (16). BUA describes a linear relationship between attenuation and frequency of ultrasound waves, and is

reported as the slope of this relationship. BUA has no direct mathematical relationship to the mechanical properties of bone: However, it is correlated with physical density of the calcaneus (45) as well as the ipsilateral femoral failure load. Other variables which may affect QUS measures include trabecular orientation and ankle edema (Lentle, personal communication).

Investigators have attempted to identify a relationship between ultrasound parameter measures and microarchitecture of bone, including trabecular and cortical bone thickness as well as connectivity of trabeculae. The one study retrieved for this assessment that investigated this question was unable to show that ultrasound measures bone microarchitecture rather than bone quantity (22).

What is the relationship between ultrasound parameters?

There is only fair correlation between BUA and SOS (r=0.57 - 0.75) (18,27,57). The calculated quantities SI and QUI are more highly correlated with BUA and SOS, as would be expected.

There are differences in the precision, change over time, and response to therapy between SOS, BUA and SI. In general, the precision error of BUA is higher than that of SOS. Due to the smaller range of physiologic values for SOS, however, the standardized coefficient of variation is similar to that of BUA. Standardizing the coefficient of variation takes into account the natural range of values for a particular measure.

Studies examining the predictive value of ultrasound with regards to fracture have used BUA, SOS and SI. Ability to predict fractures is similar for each of the three ultrasound parameters.

For a user of a method such as QUS to be able to confidently detect a change in bone density over time, it will be necessary for the precision error of the device to be lower than the change anticipated over the measurement interval. It appears that the change does not exceed the precision error for BUA over a period of one year. However, in the case of SOS and SI the change does exceed the precision error. These problems with change over time can be addressed by increasing the time between repeat tests. This limitation has implications for the use of this technology in monitoring changes in bone density. It should also be noted that QUS has only been validated in older women. Blake et al. (6) state that there are doubts as to how to interpret results in younger women.

Relationship of QUS to DXA

DXA measures the mineral content or density of bone. A recent meta-analysis of cohort studies has shown that a one standard deviation fall in bone density (BMD) at any site is predictive for a fracture at all sites, with a relative risk (RR) of 1.5 (41).

There is a higher predictive value for low bone density at a specific site and fracture at that same site. For example, measurement at the hip gives a RR for hip fracture of 2.6 for a 1 SD reduction in BMD.

All ultrasound parameters show only moderate correlation with DXA (r = 0.3 - 0.8), with correlation varying between parameters and among studies. A few studies have looked at the sensitivity and specificity of median, lower quartile, or (T score -2) values of QUS parameters in prediction of osteoporosis as defined by DXA at the spine and femur (26,54,57,80). Very low ultrasound scores (T score -2) have been used to predict osteoporosis as defined by BMD (T score -2.5) by DXA (54,57). Sensitivity for this type of comparison ranges from 88-90%.

A study that used mean ultrasound values to predict moderately low DXA in post-menopausal women showed lower sensitivity (68-70%) (80). This was similar to the results reported by Herd et al. (26) using lower quartile ultrasound parameter values to predict osteopenia as defined by a DXA T or Z score of -1. Sensitivity in that study ranged from 68-69% for lumbar spine and 63-70% for prediction of femoral neck osteopenia.

There is a general problem assessing the performance of a diagnostic test with precision errors by using another diagnostic test, which will have its own bias and precision errors. This situation results in a considerable margin of error in the prediction.

Individual QUS machines

There are a number of quantitative ultrasound QUS machines available that measure bone density at the calcaneus. The units referred to in this report were included on the basis of their documented performance and relevance to the Canadian market. There are likely other machines available in other countries that may become more prominent in the future.

The Lunar Achilles and Walker-Sonix UBA 575 devices are water bath systems. The Hologic Sahara and McCue CUBA are contact (dry) systems. The Norland Paris, although a direct contact system, is described as a contained water bath method, because the coupling medium between the heel and the transducer consists of a water reservoir.

All of these devices use paired transducers to measure the speed of sound and broadband ultrasound attenuation. The older model of Walker-Sonix 575 measured only BUA. The newer 575+ machine also measures SOS.

Status and availability:

Table 1 summarizes the status of the five machines with respect to licensing and history of use. The Hologic Sahara and Lunar Achilles both received U.S. Food and Drug Administration (FDA) pre-market approval during 1998. Both had been used previously for research purposes and marketed in a number of countries.

The Norland Paris is a machine developed by IMRO, a Canadian company. The device is being used currently for a multi-centre osteoporosis research study in Canada (CaMOS). The rights to the device were purchased by Norland, which has marketed it internationally since February 1998. It is also being distributed in the United States to be used for research purposes, as part of the FDA pre-approval process.

A 1995 review article (16) estimated that 1,700 ultrasound devices were in use world-wide. At that time their use in North America was restricted to research centres, although they were more widely distributed in Europe. A survey of BDM devices in 1996 reported the presence of 16 ultrasound machines (representing 20% of all BDM devices in the country) in Sweden and 5 ultrasound machines (4% of all devices) in Australia (40). World-wide placement of QUS devices has increased substantially over the last three years. (Siminoski, personal communication) As an illustration, a media release from Lunar in June 1998 referred to the use of more than 2,300 Achilles units in 45 countries.

Table 1: Status of QUS machines

Machine	Health Canada approval	FDA approval	History of use
Lunar Achilles	1996	1998	research use since 1991
McCue CUBA	no application	?	research use since ? 1990
Walker Sonix 575	no application	?	research use since 1988
Hologic Sahara	1996	1998	research use since 1997
Norland Paris	no application	pending	CaMOS study

Differences between machines

Two studies have compared the performance of different types of QUS machines in the same setting. The first reports precision based on measurement of a phantom (69). The short term, *in vivo* precision of the Lunar Achilles, the Walker Sonix, and the McCue CUBA were similar, with precision for BUA measurement varying from 0.75% - 1.46%. Precision data for SOS measurements showed greater variation, with values ranging from 0.25% to 2.77%. This study also compared the precision of five different Lunar Achilles machines and found a much larger range of errors (0.7%- 4.2%) than seen in an individual machine.

A study by Machado et al. (39) performed repeated measurements on osteoporotic and normal women. The precision errors were similar between the three machines, with the lowest errors (0.3% - 0.4%) being consistently associated with SOS. When precision errors were standardized for physiologic variation in the measurement , the errors for BUA and SOS were similar (9.7% - 13.2% for BUA and 5.3% - 9.7% for SOS). The magnitude of precision error was larger in this study than in the study using phantoms (69). Data for both studies are shown in Table 2.

Table 2: Analytical performance of different QUS machines

Study	Lunar Achilles	Walker-Sonix	CUBA	Hologic Sahara
Strelitzki (69) phantoms only	• CV = 0.75% for BUA, 0.25% for SOS • CV between five machines = 2.8-4.2% for BUA and 0.7% for SOS	• CV = 1.46% for BUA	• CV = 1.25% for BUA, 2.77% for SOS	
Machado (39) cross-sectional osteoporotic and normal women n=46	• CV = 0.3%(SOS), 2.6%(BUA), 2.4%(SI) • sCV = 5.3%(SOS), 9.7%(BUA), 3.5%(SI)		• CV = 0.4%(SOS), 9.4%(BUA) • sCV = 9.7%(SOS), 13.2% (BUA)	• CV = 0.3% (SOS), 5.4% (BUA), 3.5% (QUI) • sCV = 8.7% (SOS), 10.7% (BUA), 8.0% (QUI)
Greenspan (20) cross-sectional osteoporotic and normal women n=161	• CV = 2.35% (SI), SCV = 2.51% • AUC to predict DXA = 0.93(SI)	• CV = 6.64%(BUA), SCV = 5.33% • AUC to predict DXA = 0.88(BUA)	• CV = 5.21% (BUA), SCV = 4.31% • AUC to predict DXA = 0.90	

Performance of ultrasound machines

Accuracy and precision

Accuracy, or the closeness of a measurement to the true value of the attribute being measured, is difficult to define and determine for QUS. In addition, there is no way of knowing the true measure of bone density. It is possible to compare ultrasound measurements to physical properties of bone in cadaveric studies, or examine the ability of QUS to discriminate between osteoporotic individuals (with fracture) and normals. However, these are intermediary comparisons and do not represent true accuracy.

Precision (reproducibility) is good when the random error is low, making the variation between measurements on the same sample small (21). Short term precision is usually measured by performing repeated studies on a group of individuals, and calculating the coefficient of variation. Some studies report the correlation between the first and second measurement instead of coefficient of variation as their measure of precision. Long term precision relates to the variation of measurements over time. This precision measurement provides information needed to assess the reliability of the device to perform follow-up examinations. There are few data published on long term precision.

Issues that may affect the accuracy and precision of QUS at the calcaneus include: handedness (29), water bath temperature (48), ankle edema (30), volume of fatty tissue (33) and the use of tap water rather than pre-boiled water (14).

Most of the studies using the Walker Sonix machine report only BUA, as SOS was only available in the later model. There is no information on the accuracy of this device. Short term precision of the BUA measurement varies from 2.1 - 6.6% (3-5,8-10,24,29,36,43,51,57,63). One study looked at long term precision over 1 year (67) and reported a value of 3.3%.

The Lunar Achilles reports BUA, SOS, and SI. Precision values are available for all three measurements. In general, the precision error of the SOS is smaller than that for BUA. Results from a number of studies indicate that the coefficients of variation vary from 0.15% - 0.7% for SOS, from 0.4% - 3.0% for BUA, and from 0.2% - 3.0% for SI (20,38,45,47,52-54,64,65,67). Two studies report the standardized coefficient of variation, where the CV has been standardized for the physiologic range of values. The standardized CV for SOS, BUA, and SI vary from 5.3% - 6%, 6.1% - 9.7%, and 3.5% - 4.5% respectively (39,75).

The McCue company has produced both the CUBA clinical and the CUBA research machines. Most clinical studies report results on the CUBA clinical device. Short term precision for the BUA measurement varies from 2.5% - 3.8%

(1,15,35). The velocity measurement had CVs of 0.44% - 1.4% (1,19,42). One study reported precision over three months, giving values of 4.9% for BUA and 1.3% for SOS (19). There are no reports of standardized coefficient of variation for either measurement. A study on the CUBA research model reported short term precision values of 6.3% for BUA and 1.04% for heel velocity (27).

The Hologic Sahara has the least amount of documentary evidence for its performance. Three cross-sectional studies were located, presented as abstracts, that reported data on short term precision (31,39,65). The coefficient of variation reported for BUA ranged from 3.0% - 5.4% and the values for SOS range from 0.18% - 0.3%. One study reports standardized coefficients of variation for BUA and SOS, of 10.7% and 8.7% respectively (39).

A guide in evaluating the utility of a diagnostic technology is that the error of the measurement must be smaller than the expected change which is to be identified. If QUS is to be used for the diagnosis of osteoporosis, the precision error needs to be smaller than the difference between osteoporotic and normal values (2). For use in monitoring, the precision error should be smaller than the expected change in values during the interval between measurements.

Two studies have evaluated this aspect of QUS performance (62,75). Schott et al. showed that the expected change in ultrasound parameters in post-menopausal women over two years was equivalent to five times the precision error for SOS and equal to the precision error for BUA (62). van Daele et al. calculated how much of the variation of change in ultrasound parameters over approximately 1.5 years of follow-up was attributable to the measurement error. For SOS it was 27%, while for BUA it was 9% (75). They also calculated the time between measurements that would be required to be confident of identifying a true change in the parameter. In their cohort, both SOS and SI decreased significantly (beyond precision error) within 1.4 years. Their patient group did not experience a significant change in BUA over the study period (2 years).

Comparing these results to the precision errors for DXA, it is apparent that the errors are higher for QUS. Reported short term precision errors for DXA measurement of the spine range from 0.9% - 1.33%, for femoral neck, 1.2% - 3.2%, for Ward's triangle, 2.5% and for trochanter, 2.5% (36,47,52,64). Precision data for the QUS machines are summarized in Table 3. Further details of studies on the performance of these QUS devices are given in Appendix B.

Table 3: In vivo precision data for QUS machines [1]

Machine	BUA	SOS	SI
Walker Sonix	2.1 - 6.6% 3.3% (long term)	N/A	N/A
Lunar Achilles	0.4 - 2.8%	0.15 - 0.7%	0.2 - 3.0%
McCue CUBA clinical	2.5 - 3.8% 4.9% (long term)	0.4 - 1.4% 1.3%	N/A
McCue CUBA research	6.3%	1.0%	N/A
Hologic Sahara	3.0 - 5.4%	0.18 - 0.3%	N/A

(1) All values represent short term coefficient of variation unless otherwise indicated

Ability to predict fractures

Data on prediction of fracture risk for three machines are summarized in Table 4.

Results from most studies indicate good correlation of ultrasound parameters with fracture prevalence. The relative risk of fracture associated with a decrease in the ultrasound measurement are of the same order as those associated with a decrease in the DXA measurement at the spine and hip, although somewhat lower. Reported relative risks are either unadjusted, adjusted for age, or adjusted for age and DXA.

The Walker Sonix 575 machine was used in three prospective cohort studies that examined the predictive value of QUS with regards to hip and other fracture. One reported a RR for hip fracture of 2.0 (95% CI 1.5,2.7) and a RR for all fractures of 1.3 (95% CI 1.2,1.5) (4). Another study reported a RR for all fractures of 1.4 (95% CI 1.2,2.4) (68). All of these RR values are based on a one standard deviation (SD) fall in BUA for that population (peri- and post-menopausal women). The first two estimates are adjusted for age, and the third is unadjusted.

One of the most quoted papers describes a prospective cohort study of elderly women in nursing homes (53). While it does not report RR, it clearly outlines the different fracture risks for groups of women based on their BUA measurement, level of cognizance and mobility. In women with the highest BUA values and levels of cognizance, the fracture rate was 1.5% over 2 years, compared to a fracture rate of 12.8% in women with the lowest BUA and cognizance. On the other hand, in women with high mobility and cognizance there was minimal difference in fracture risk on the basis of the BUA value (0.9% as compared to 1.2%). These results bring home the point that bone density plays a role in fracture

prediction, but is by no means the sole contributor to fracture risk. Furthermore, it is apparent that, depending on the presence or absence of other risk factors, bone density may be highly predictive or not predictive at all.

Fracture prediction by the Lunar Achilles is reported in two of the six prospective studies which used this machine. One reports RR for hip fracture of 1.9 (95% CI 1.5,2.3) for SOS and 2.1(95% CI 1.7,2.6) for BUA (23). Both of these RR values are unadjusted, and refer to ultrasound values below the median for the population (elderly women). The other study reported in abstract form, does not cite RR values, but only the proportion of incident fractures that occurred in the groups with the highest (16.4%) and lowest (37.7%) quartile of stiffness index for that population (post-menopausal women) (71).

There are limited data regarding fracture prediction available for the CUBA clinical machine. One prospective study presented in abstract form was conducted in 710 elderly women. There were BUA and SOS measurements and a 2 year follow-up (50). BUA was able to predict hip fractures, with a RR of 4.5 (95% CI 1.1, 16.5). This relative risk value compared the women with BUA scores in the lowest tertile to those with values in the highest tertile. This may partially account for the high RR value. SOS was not able to predict hip fractures, and neither measurement was predictive of other osteoporotic fractures. One cross-sectional study reported fracture information, but simply stated that the median BUA and SOS values were lower in the group with a fracture history (19).

A cross-sectional study that utilized the Hologic Sahara found that mean values for all ultrasound parameters were lower in patients with a history of fracture, compared to those without (31). In their promotional material, Hologic state that the Sahara can be used to predict fractures on the basis of the high correlation of its measurements with those of the Walker Sonix machine: “Sahara and Walker Sonix results were highly correlated (r=0.91), indicating that results of previous, large prospective fracture risk studies…are applicable to Sahara”. This was reported despite the fact that the Hologic is a dry system and the Walker Sonix is water bath-based. Direct evidence regarding the predictive value of the Hologic Sahara is still required.

Avecilla et al. state in their review, that while the water-based calcaneal ultrasound devices have demonstrated acceptable sensitivity in predicting spine and hip fractures, other methods have not been widely validated. (2).

Some studies perform receiver operating characteristic (ROC) analysis which combines the sensitivity and specificity of a test, in this case to predict fractures. The ideal test has a calculated area under the curve (AUC) with a value close to one, indicating high sensitivity and high specificity.

There are 4 studies utilizing the Walker Sonix machine that report ROC data. All use the BUA parameter, and report an AUC of 0.76 for predicting hip fractures (67), 0.56 - 0.79 for vertebral fractures (59,66) and 0.58 for prediction of all fractures (68).

There are 3 studies reporting AUC for fracture prediction using the Achilles machine. For hip fractures the AUC's range from 0.75 - 0.85 for SOS and 0.77 - 0.79 for BUA (64,72). For vertebral fractures the corresponding values are 0.68 - 0.81 for SOS and 0.66 - 0.78 for BUA (18,72). It is difficult to compare results from different studies, however, due to differences in patient characteristics and study methodology.

Ultrasound appears to be a promising tool in the prediction of fractures for a population, even controlling for age. However, fracture prediction for an individual would be subject to the same types of limitation described for DXA (41) An issue here is that fracture risk for an individual is linked to multiple risk factors.

Some of the studies report a statistically significant predictive ability of ultrasound even after adjusting for BMD as measured by DXA (4,5,17,18,23,58,72). All analyses utilized logistic regression models, which evaluated the ability of ultrasound parameters, BMD and age to predict fractures. These analyses generate a relative risk estimate for each predictor variable, which is adjusted for the other two variables. All studies showed that there was a statistically significant increase in risk of fracture for a low ultrasound value (mostly BUA), even when the femoral or lumbar BMD was taken into account. The range of relative risks was 1.1 - 1.6 (4,5,17,58,72). One study reported a higher RR of 2.0. This may be because the outcome was vertebral deformity and not symptomatic hip or vertebral fracture.

Although these results imply that DXA and QUS identify different groups of people, there is no evidence of increased "capture" if both tests are performed (17).

Most of the studies performed to evaluate fracture risk were cross-sectional and do not provide the same level of evidence as prospective cohort studies. Results from cross sectional studies are summarized in the tables in Appendix B.

Cut-off values for QUS used in the relative risk calculations are variously reported as median, lowest tertile, or lowest quartile. It is unlikely a discrete value for SOS and BUA could be identified that could be used for all populations in determination of fracture risk. It seems likely that cut-off points would need to be determined for individual machines, similar to those used for the different DXA machines.

In summary, there is good evidence that quantitative ultrasound is able to identify populations of women at increased risk of both vertebral and hip fracture. Its

ability to predict fractures in an individual rather than a population is less clear (as in the case with risk factor assessment in general). The etiology of osteoporotic fractures is multifactorial and it is not possible to precisely identify at risk individuals with BMD measurement alone.

Table 4: Prediction of risk of fracture by QUS

Machine	Parameter	RR at the hip	RR all sites	AUC for hip fracture	AUC for vertebral fracture
Walker Sonix	BUA	2.0[a] (1.5 - 2.7)	1.3[a] (1.2 - 1.5) 1.4[ab] (1.2 - 2.4)	0.76	0.56 - 0.79
Achilles	SOS	1.9[bc] (1.5 - 2.3)		0.75 - 0.85	0.68 - 0.81
	BUA	2.1[bc] (1.7 - 2.6)		0.77 - 0.79	0.66 - 0.78
CUBA	SOS	not predictive	not predictive		
	BUA	4.5[d] (1.1 - 16.5)			

a - relative risk is age adjusted
b - relative risk is not age adjusted
c - for ultrasound values below the median
d - comparing lowest tertile to highest tertile

Evidence of clinical utility

There is no evidence that the use of QUS appropriately influences management decisions or improves health outcomes. Research regarding use of ultrasound technology to measure bone density seems to be at an early stage, involving mainly evaluation of the performance of the various machines.

Two papers by Langton et al. describe evaluation of the role of ultrasound in routine clinical practice (36,37). The use of clinical criteria was compared to BUA measurement as a prescreen for DXA (37). One hundred and seven post-menopausal women underwent BMD measurement by DXA and QUS (CUBA Clinical), as well as filling out a questionnaire to determine the presence of risk factors. Risk factors included osteopenia on x-ray; underlying disease associated with osteoporosis; treatment with corticosteroids; premature menopause and positive family history. Langton et al. calculated the cost to correctly identify an osteoporotic person (as defined by DXA). They report that identifying a low BUA measurement (60db/MHz) was a more cost-effective method of predicting osteoporosis by DXA than the clinical criteria. The study is limited by the use of an unvalidated set of clinical criteria.(not developed to predict DXA measurement). More studies of this sort are needed to help define the role of QUS in osteoporosis diagnosis and management.

The role of QUS in the diagnosis of osteoporosis

Pre-screening tool prior to DXA

It has been suggested that QUS could be used as a low cost way to pre-screen women to reduce the number of BMD measurements performed by DXA. The poor correlation of the ultrasound parameters with BMD measurement with DXA, however, makes this application impractical. There is controversy on this point, as portrayed in the medical literature. Popcock et al. state that estimates of error were too large for QUS to be used to predict BMD (51). Others consider that QUS could be a cost-effective method to pre-screen patients for DXA, when compared to clinical referral criteria (37). This second proposition depends on the validity of the clinical criteria, as well as the cost of the QUS and DXA procedures. Another issue associated with use of two diagnostic tests is that their measurement errors will be additive, which may decrease the reliability of the bone density value.

QUS cannot be recommended for use as a pre-screening tool for the general population (with subsequent confirmation by DXA) for the purposes of diagnosing osteoporosis. Use of a combined strategy of this sort would increase costs, and cost-effectiveness would be a concern.

Use of ultrasound instead of DXA in under-serviced areas

A number of studies have shown that the predictive power for QUS is of the same order as that of DXA (though the x-ray method is superior). If this is confirmed in more rigorous prospective trials, then QUS might be used instead of DXA for the purposes of fracture prediction. The use of quantitative calcaneal ultrasound in areas where DXA is not available is a potential option, though this could effectively be equivalent to that considered under the "pre-screening" scenario.

DXA is often used to monitor response to therapy with bone sparing agents. Although there are limitations in this application due to the precision errors of this technology, these are well known, and can be taken into account by less frequent monitoring. QUS, on the other hand, does not have the same track record in long term follow-up of osteoporosis treatment. More work needs to be done to determine if QUS can accurately reflect changes in bone density over time, or whether such changes are beyond the precision error of the technology .

Practical matters to consider are:

- Whether patients diagnosed with osteoporosis on the basis of QUS would then need a confirmatory test (DXA measurement)
- Whether monitoring of patients would have to be done using DXA technology, because of the precision limitations of QUS.
- The considerable potential for duplication of services.

Use in combination with DXA for better fracture prediction

A few of the studies that have looked at the ability of QUS to predict fractures have also examined the significance of confounding predictive factors. These include age of the patient, weight and BMD as measured by DXA. These studies show that the predictive value of QUS is still significant, even after taking these factors into account. This finding has led investigators to propose that QUS measures something different than DXA, perhaps the structural quality of bone.

If this is true, then perhaps the combined investigations of DXA and QUS would provide stronger predictive information. This premise has been tested in one study. Glüer et al.. showed that combining the results of DXA and BUA measurements of the femur did not increase the area under the receiver operating characteristic, unless the specificity of the procedures was high (80% - 95%) (17). This study showed that knowing the BUA value as well as the DXA value did not provide additional predictive power to that from the DXA measurement alone. There is no evidence to support increased diagnostic yield by using two tests instead of one.

Discussion

Other data needed to draw conclusions

There are multiple factors that put a person at risk for vertebral and hip fracture. It is naïve to assume that knowledge of DXA or QUS data will allow accurate prediction of fracture risk in an individual. These are useful methods to diagnose osteoporosis, but not all people with osteoporosis suffer a fracture. As previously described, Porter et al. showed that low BUA, poor cognition and good mobility were all significant predictors of hip fractures in nursing home residents (53). These factors interacted in different ways to give a strong association with fracture. For example, if a patient was not mobile, then BUA was not associated with risk of fracture. In patients who were mobile with poor cognition, a low BUA added an extra risk for fracture. More research of this type needs to be done to look at the multifactorial nature of osteoporotic fracture.

There is also need for more information regarding the ability of QUS to identify small changes in the ultrasound parameters over time. There may be situations where large changes in bone density are anticipated or less frequent monitoring could be used to compensate for the limitations in precision.

The implications for Alberta of the introduction of this technology are unclear. If QUS was adopted by health care providers, there would be costs related to the utilization of a new procedure and possibly more diagnoses of osteoporosis than there are currently. This could lead to increased prescription rates for anti-resorptive therapy. There is a potential to increase the number of women tested for osteoporosis if a method is available that is convenient, easy to use and more accessible to the rural patient.

The level of use of QUS would in part depend on the current practice patterns of utilization of existing BMD measurement technologies. There are no published data regarding the current use of bone density technologies among physicians in Alberta, but a recent study looking at attitudes of Alberta physicians regarding the diagnosis and treatment of osteoporosis showed significant practice pattern variation (70). A concern would be that such management decisions would be based on results from a technology whose analytical performance is still poorly defined in routine practice. Available data indicate that, as with other methods such as DXA, there would be a high proportion of both false positive and false negative results. Depending on the presence or absence of guidelines, this could also lead to the increased utilization of existing BMD technologies for confirmation of the ultrasound result.

Finally, research would be needed to answer the question of whether QUS was changing the way osteoporosis was being diagnosed and treated, and whether health outcomes for persons with this condition had improved.

Quantitative calcaneal ultrasound appears to be a promising diagnostic technology, based on early research findings. It is, however, less well established than the widely used x-ray techniques. Its role in the diagnosis of osteoporosis remains unclear.

The evidence supporting the clinical utility of QUS is still preliminary and limited. The quality of evidence for the performance of this device, using published criteria on levels of evidence (81) is no better than fair to poor. Further evidence regarding long term precision, prospective prediction of osteoporosis and fractures, and use in following patients on therapy are needed before the place of this technology in routine health care can be determined.

There are not many types of QUS machines on the market currently, but this situation may change. Those machines that have been studied extensively and

reported on in the literature are not the same devices that are now being marketed aggressively. Further, good quality, studies on current QUS devices on the market would be highly desirable. Issues of product regulation and quality control are not well developed at this point. From the information available for this assessment, the value of QUS to health care is still unclear. In this rapidly evolving field, the technical performance of QUS technology and its role in routine clinical practice will need to be kept under review.

Appendix A - Methodology

Literature searches were conducted for the years 1988 - 1998 on the following electronic databases: Medline, EMBASE, HealthSTAR and Current Contents. Search terms used included: calcaneal ultrasound.ti, ab, sh., exp Calcaneus/, exp densitometry/, exp osteoporosis/ or exp osteoporosis, postmenopausal/, exp Mass screening/, exp Bone density/, ultrasonography/. These terms were used singly and in various combinations. Abstracts presented at the most recent meetings of the American College of Rheumatology and the American Society for Bone and Mineral Research were hand searched for relevant studies. Reference lists of retrieved articles were also hand searched for studies that were missed by the electronic searches.

Appendix B: Studies using QUS machines

Table 5: Walker Sonix

Author	Precision	Predicting DXA	Predicting Fractures
Porter 1990 (53) prospective cohort, institutionalized elderly women n= 1414 Osteosonics UBA1001 BUA			• compares the women who sustained a hip fracture during the 2 year follow-up period to those that did not • BUA expressed as low, med, high • cognizance = low, med, high • BUA sig lower in fracture patients • 52% of fractures occurred in women with BUA in the lowest tertile • women with high BUA and good cognizance, fracture risk = 1.5% women with low BUA and low cognizance , fracture risk = 12.8%
Bauer 1995 (5) cross-sectional FIT study	• CV over 1-4 weeks was 5.8% • "averaging over 3 consecutive readings improved precision to 4%"		RR of vertebral fracture for 1 SD drop in BUA • 1.6 (1.3,2.1) unadjusted • 1.5 (1.1,2.0) adjusted for age, weight, spinal BMD, and centre
Bauer 1997 (4) prospective cohort post-menopausal women SOF study	• CV 4.1%-5.6% for 4 sites	• correlation between BUA and DXA femoral neck = 0.42 • correlation between BUA and DXA calcaneus = 0.70	• RR of hip fracture for 1 SD fall in BUA = 2 (1.5,2.7) adjusted for age; 1.5 (1,2.1) adjusted for age and femoral BMD 1.3 (0.8,2.1) adjusted for calcaneal BMD • RR of all non-spine fracture for 1 SD fall in BUA 1.3 (1.2,1.5) adjusted for age; 1.2 (1.1,1.4) adjusted for femoral BMD; 1.1 (0.9,1.3) adjusted for calcaneal BMD
Ross 1995 (58) post-menopausal women Japanese origin	• reproducibility 3.6 dB/MHz	• correlation BUA and DXA spine = 0.43 • correlation BUA and DXA calcaneus = 0.68	• OR of vertebral deformity for 1sd fall in BUA =1.8(1.35,2.4) adjusted for age; 1.57 (1.15,2.13) adjusted for spine BMD; 1.49 (1.03,2.15) adjusted for calcaneal BMD
Gluer 1996 (17) retrospective cohort study of osteoporotic fractures post-menopausal women n=4,698			• OR for 1 SD fall in BUA =1.9 (incident hip), 1.7 (incident vert) adjusted for age, centre, machine • OR for 1 SD fall in BUA =1.9 (hip), 1.5 (incident vert) adjusted for age, centre, machine and femoral neck BMD • AUC for hip fracture = 0.723, for vertebral fracture = 0.641 • combined AUC larger than AUC for BMD hip alone only at high specificities
Poet 1994 (52) cross-sectional mixed study sample	• CV = 6.09% • mean % difference between right and left calces = 6% • mean % difference between right and left femora = 2% (DXA)	• correlation BUA and DXA spine = 0.81 • correlation BUA and QCT spine = 0.53	• mean BUA in vertebral fracture group was not different from control group
Stewart 1994 (67) case control	• CV 2.6% • CV 3.3% over 1 year		• ROC curve for BUA and DXA in predicting hip fractures • BUA with best AUC
Stewart 1995 (66) cross-sectional EVOS study	• as above		• ROC for BUA and DXA in predicting vertebral fractures • DXA hip with best AUC, BUA with worst
Dretakis 1994 (12) case control	• CV 3.8%		• sens and spec for fractures for BUA = 61dB/MHz (97%&72%) • sens and spec for fractures with BUA = 51dB/Mhz (70%&92%)
Stewart 1996 (68) population based prospective cohort peri-menopausal women	• as above		• OR of any fracture for I SD fall in BUA = 1.4(1.2,2.4) unadjusted • ROC curve for BUA and DXA DXA spine with best AUC
Brooke-Wavell 1995 (8) cross-sectional post-menopausal	• CV = 6.6%	• correlation BUA and DXA spine = 0.39 • correlation BUA and DXA calcaneus = 0.66 • correlation BUA and DXA femoral neck = 0.40	
Baran 1988 (3)	• CV = 2.6%	• correlation BUA and DPA spine = 0.607	• ROC curve for BUA to predict vertebral fracture and osteopenia, as

Table 5: Walker Sonix

Author	Precision	Predicting DXA	Predicting Fractures
cross-sectional		• correlation BUA and DPA femoral neck = 0.594	well as hip fracture
Herd 1992 (28) cross-sectional mixed young, old and osteoporotic women	• short term precision (young normals) CV=4.2% • short term precision(mixed normal) CV=4.6% • correlation between heels=0.86		• mean BUA lower in women with vertebral fracture (?stat sig)
Massie 1993 (43) population based sample peri-menopausal women n=1000 cross-sectional	• short term CV = 2.6% for BUA • in vivo short term precision DXA CV = 0.9%(spine) and 2.4%(hip)	• correlation BUA and DXA spine = 0.328, DXA femoral neck = 0.294, DXA trochanter = 0.354, DXA Ward's triangle = 0.282	
Kroger 1995(35) case control mixed study sample	• short term CV 3.5%	• correlation BUA and DXA spine = 0.34 • correlation BUA and DXA femoral neck = 0.43	• mean BUA in fracture group less than normals (not matched for age)
Vahlensieck (73) ?cross-sectional women n=54	• CV = 2.1%	• correlation BUA and DXA spine = 0.5	
Salamone 1994 (61) cross-sectional post-menopausal	• CV = 3.6±3.5%	• correlation BUA and DXA spine = 0.43 • correlation BUA and DXA femoral neck = 0.43 • correlation BUA and SXA calcaneus = 0.66	
Young 1993 (80) cross-sectional peri-menopausal women n=578	• in vitro precision analysis only	• correlation BUA and DXA spine = 0.40, DXA femoral neck = 0.35 • median BUA predicts lower quartile:DXA spine sens = 70% spec = 65%; DXA femoral neck sens = 68% spec = 64%	
Evans 1995 (14) case series UBA 1001	• CV = 0.9-3.1% for normal tap water • CV = 1.0-2.6% for pre-boiled water • machine takes repeated measurements until 3 consecutive stable values, then averages • BUA varies most with foot position and rotation during scanning		
Dretakis 1995 (13) case control post-menopausal			• mean BUA in hip fracture group less than controls, even matched for age
Dretakis 1994 (11) cross-sectional mixed age women	• CV = 3.8±1.4% • mean % difference between right and left calces = 7.3-7.7%		
Roux 1993 (59) cross-sectional mixed age women	• CV = 2.85±1.68% • mean individual differences between calces = 8.5±6.8%	ROC for predicting osteopenia	• ROC for predicting vertebral fracture

21

Table 6: Lunar Achilles

Author	Precision	Predicting DXA	Predicting Fractures
Hans 1996 (23) prospective cohort, EPIDOS study (elderly women)			
1. speed of sound	• CV = 0.2%		• RR for hip fracture = 1.9 (1.5,2.3) unadjusted • RR for hip fracture = 1.4 (1.1,1.8) adjusted for age, wt, femur BMD
2. BUA	• CV = 1.8%		• RR for hip fracture = 2.1 (1.7,2.6) unadjusted • RR for hip fracture = 1.7 (1.4,2.2) adjusted for age, wt, femur BMD
Schott 1995 (62) prospective cohort n=113 samples from EPIDOS and OFELY(post-menopausal)	DXA in vivo precision at femoral neck =1.7% (Lunar), and 1.2% (Hologic)	%Δ DXA femoral neck over 2 years = 1.85%(4.4) corresponding to 1x precision error	
1. speed of sound	• CV = 0.17%(0.03) • %Δ over 2 years = -0.8(0.6) corresponds to 5x precision	• correlation between %Δ SOS and %Δ DXA = 0.20	
2. BUA	• CV = 1.2%(0.21) • %Δ over 2 years = -1%(4.3) corresponds to 1x precision	• correlation between %Δ BUA and %Δ BMD = 0.25	
3. stiffness index	• CV = 1.3%(0.3) • Δ over 2 years = -3.8(14.2) corresponds to 2.5x precision	• correlation between %Δ SI and %Δ BMD = 0.31	
Schott 1995 (64) case control, post-menopausal			
1. speed of sound	• CV = 0.17%	• correlation with DXA femoral neck=0.4	AUC from ROC = 0.75 =/-.04
2. BUA	• CV = 1.17%	• correlation with DXA femoral neck=0.49	AUC from ROC = 0.77+/-.04
3. stiffness index	• CV = 1.32%	• correlation with DXA femoral neck=0.46	AUC from ROC = 0.78+/-.04
4. DXA	• CV =1.2% femoral neck • CV = 2.3% ward's • CV = 1.5% trochanter		AUC from ROC = 0.74+/-.04

Table 6: Lunar Achilles

Author	Precision	Predicting DXA	Predicting Fractures
van Daele 1997 (75) prospective cohort n=543 men and women	short term precision Graph of number of years necessary to state that change in US is not attributable to measurement error		
1. speed of sound	• CV = 0.5%, sCV = 6.0% • %Δ/year = -1.9 to -2.2 (sig) • 27% of variation in Δ explained by measurement error	no statistically significant correlation between rate of QUS change and rate of change in DXA	
2. BUA	• CV = 2.3%, sCV = 6.1% • %Δ/year = 0.05 to 0.09(non sig) • 9% of variation in Δ explained by measurement error	no statistically significant correlation between rate of QUS change and rate of change in DXA	
3. stiffness index	• CV = 3.0%, sCV = 4.5% • %Δ/year = -0.77 to -0.9 (sig) • 11% of variation in Δ explained by measurement error		
van Daele 1994 (74) cross-sectional population based cohort elderly, M and F n=1405	Results of in vivo precision for DXA • CV L-spine = 0.9%, femoral neck = 3.2%, Ward's = 2.5%, trochanter = 2.5%		• reports percentage overlap in patients with lowest quartile US and DXA
1. speed of sound	• CV = 0.45%	• corr DXA spine = 0.33 (men) = 0.42 (women) • corr DXA femoral neck = 0.37 (men) = 0.49 (women) • corr DXA Ward's = 0.38 (men) = 0.5 (women) • corr DXA trochanter = 0.43 (men) = 0.48 (women)	
2. BUA	• CV = 2.28%	• corr DXA spine = 0.32 (men) = 0.37 (women) • corr DXA femoral neck = 0.34 (men) = 0.43 (women) • corr DXA Ward's = 0.35 (men) = 0.44 (women) • corr DXA trochanter = 0.39 (men) = 0.42 (women)	
Gonnelli 1995 (18) cross-sectional, women referred for screening n=304			ROC show DXA spine BMD superior to QUS
1. speed of sound	• correlation with BUA = 0.57	• correlation with DXA spine = 0.54	• OR for vertebral fracture = 4.55 unadjusted; 2.27 adjusted for spine BMD only
2. BUA		• correlation with DXA spine = 0.45	• OR for vertebral fracture = 3.1 unadjusted; 2.0 adjusted for spine BMD only
3. stiffness index		• correlation with DXA spine = 0.56	• OR for vertebral fracture = 4.8 unadjusted; 2.8 adjusted for spine BMD only.

Table 6: Lunar Achilles

Author	Precision	Predicting DXA	Predicting Fractures	
Thompson (71) prospective cohort n=1857			37.7% of incident fractures occurred in women with the lowest quartile of age-adjusted stiffness, compared to 10% in the highest quartile	
Turner 1995 (72) cross-sectional elderly women n=336			AUC for predicting fractures with and without BMD (at same site) HIP FRACTURE	SPINE FRACTURE
1. speed of sound		• corr with DXA spine = 0.4, DXA femoral neck =0.48	0.85/0.87	0.68/0.71
2. BUA		• corr with DXA spine = 0.43, DXA femoral neck = 0.54	0.79/0.82	0.66/0.68
3. stiffness index		• corr with DXA spine = 0.43, DXA femoral neck = 0.53	0.83/0.85	0.70/0.72
Giorgino 1997 (82) CCT with clodronate			Response to therapy	
1. speed of sound (normalized)			• %Δ in treated = 0 • %Δ in controls = -3.5%/2 years	
2. BUA (normalized)			• %Δ in treated = 1.6-1.9%/2years • %Δ in controls = -3.2%/2years	
Rosenthall 1995 (57) cross-section n=1000 mixed women		report sens & spec of US in predicting BMD<-2 at spine, femoral neck, and ward's		
1. speed of sound		• corr DXA spine = 0.55, femoral neck = 0.54, ward's = 0.56		
2. BUA		• corr DXA spine = 0.54, femoral neck = 0.55, ward's = 0.55		
3. stiffness index		• corr DXA spine = 0.59, femoral neck = 0.6, ward's = 0.61		
Rosenthall 1996 (56) cross-sectional n=220 peri or post-menopausal	Results of in vivo precision for DXA • CV = 1.33% (spine) and 2.84% (femoral neck)			
1. speed of sound	• CV = 0.24%	• corr DXA spine = 0.59 • corr DXA femoral neck = 0.54	• not sig lower in fracture group (controlled for age)	
2. BUA	• CV = 2.75%	• corr DXA spine = 0.57 • corr DXA femoral neck = 0.52	• sig lower in fracture group (controlled for age)	
3. stiffness index	• CV = 2.64%	• corr DXA spine = 0.63 • corr DXA femoral neck = 0.58	• sig lower in fracture group (controlled for age)	
Rosenthall 1997 (55) cross-sectional normal and osteoporotic women				
1. speed of sound	• median CV (normals)= 0.23% • median CV (osteopor)= 0.19%			
2. BUA	• median CV (normals) = 1.99% • median CV (osteopor) = 1.44%			
3. stiffness index	• median CV (normals) = 2.15% • median CV (osteopor) = 2.02%			

Table 6: Lunar Achilles

Author	Precision	Predicting DXA	Predicting Fractures
Kolthoff Acta 1995 (32) cross-section ?case control		data for normals only	
1. stiffness index	• short term precision <2% • corr rt & left = 0.9(normals) • corr rt & left = 0.71(hip # patients)	• corr DXA spine = 0.46 • corr DXA femoral neck = 0.62 • corr DXA Wards = 0.51 • corr DXA trochanter = 0.72	
Hans 1994 (25) young normals and 15 elderly from EPIDOS	data an average from five centres long term = 12 months		
1. speed of sound	• in vivo short term CV = 0.23% • in vitro long term CV = 0.32%		
2. BUA	• in vivo short term CV = 1.83% • in vitro long term CV = 1.42%		
3. stiffness index	• in vivo short term CV = 1.9% • in vitro long term CV = 2.33%		
Chow 1996 (9) Spinal cord injury patients n=31 and volunteers n=79			
1. speed of sound		• corr DXA spine =-0.69,DXA femoral neck = 0.66, DXA Ward's = 0.74, DXA trochanter = 0.48	
2. BUA		• corr DXA spine =-0.54, DXA femoral neck = 0.62, DXA Ward's = 0.69, DXA trochanter = 0.39	
3. Stiffness index	• mean z score and mean % difference from normals increased with increasing time from injury	• corr DXA spine =-0.67, DXA femoral neck = 0.69, DXA Ward's = 0.77, DXA trochanter=0.47	
Sakata 1997 (60) Case control Japanese women			
1. speed of sound	• CV = 0.3%		• OR for hip fracture= 2.51(1.78,3.54) unadjusted
2. BUA	• CV= 1.0%		• OR for hip fracture = 3.24(2.29,4.6) unadjusted
3. stiffness index	• CV = 0.6%		• OR for hip fracture = 3.6(2.48,5.22) unadjusted
Faulkner 1994 (15) cross-sectional post-menopausal n=170	Based on single healthy volunteers		
1. speed of sound	CV = 0.5% corr with BUA = 0.552	• Corr DXA spine = 0.49, DXA femoral neck = 0.5, DXA Ward's = 0.48, DXA trochanter = 0.49	
2. BUA	• CV = 1.8%	• corr DXA spine = 0.46, DXA femoral neck = 0.42, DXA Ward's = 0.33, DXA trochanter = 0.4	
3. stiffness index	• CV = 2.14%	• corr DXA spine = 0.55, DXA femoral neck = 0.55, DXA Ward's = 0.48, DXA trochanter = 0.52	
	•	•	

Table 6: Lunar Achilles

Author	Precision	Predicting DXA	Predicting Fractures
Hans 1995 (24) Cross-sectional Mixed women n=271	• short term precision • significantly predicted by heel width (precision implications)	• in vivo DXA precision = 2.4%(femoral neck) and 0.9%(lumbar spine) for Lunar and 1.8% (femoral neck) and 0.9% (lumbar spine) for Hologic	
1. speed of sound	• CV = 0.17%		
2. BUA	• CV = 1.17%		
3. stiffness index	• CV = 1.32%		
Moris 1995 (47) Cross-sectional M and F no fractures			
1. speed of sound	• CV (same day) = 0.2% • CV (6mo) = 0.3% • correlation rt and left foot = 0.98	• correlation with DXA spine = 0.49	
2. BUA	• CV (same day) = 1.6% • CV (6mo) = 1.7% • correlation rt and left foot = 0.95	• correlation with DXA spine = 0.5	
3. stiffness index	• CV (same day) = 1.1% • CV (6mo) = 1.9% • correlation rt and left foot = 0.98	• correlation with DXA spine = 0.53	
Krieg 1996 (34) Cross-sectional Elderly women, institutions	?long term precision repeated measurements after 1 year		all measures were stat sig lower in group with history of non-vertebral fractures (corrected for age)
1. speed of sound	• mean % change= -0.31% (sig)		
2. BUA	• mean % change=0.98% (nonsig)		
3. stiffness index	• mean % change= -3.6% (sig)		
Naessen 1995 (49) case control post-menopausal ½ on HRT	• short term precision	DXA measured at spine, femoral neck, Ward's, trochanter	
1. speed of sound	• CV = 0.18%	• corr with DXA in non HRT users = 0.51-0.59 • corr with DXA in HRT users = 0.16-0.31 • % difference between groups = 1.1%	In multiple regression modeling, with age and years of therapy predicting US, US decreases with increasing time on therapy. This was a case control study and not a prospective collection of data.
2. BUA	• CV = 1.3%	• corr with DXA in non HRT users = 0.50-0.61 • corr with DXA in HRT users = 0.005-0.27 • % difference between groups = 6.1%	
3. stiffness index	• CV = 1.5%	• corr with DXA in non HRT users = 0.52-0.61 • corr with DXA in HRT users = 0.1-0.31 • %difference between groups = 12%	

Table 6: Lunar Achilles

Author	Precision	Predicting DXA	Predicting Fractures
Rosenthall 1997 (54) case series n=2500 mixed women		sensitivity and specificity of the stiffness index for predicting a T score of -2.5 by DXA	
1. stiffness index		• SI T score of -2.5: sens = 76.3% and spec=69.9% (lumbar); sens = 82.1% and spec = 62.5% (femoral neck)	
Schott 1993 (63) cross-sectional n=512 mixed women	short term precision		
1. speed of sound	• CV = 0.15%(0.03) • represents 7% of the biologic variation observed	• corr with Hologic DXA (femoral neck) = 0.348 • corr with Lunar DXA (femoral neck) = 0.288	
2. BUA	• CV = 0.93%(0.21) • represents 9.6% of the biologic variation observed	• corr with Hologic DXA (femoral neck) = 0.41 • corr with Lunar DXA (femoral neck) = -0.322	
Lees 1993 (38) cross-section random sample of women	• short term precision		
1. speed of sound	• CV(normals)=0.19% • CV(osteopenic)=0.13%	• corr DXA spine = 0.54 • corr DXA femoral neck = 0.65 • corr DXA Wards = 0.62 • corr DXA trochanter = 0.58	
2. BUA	• CV(normals)=1.38% • CV(osteopenic)=1.09%	• corr DXA spine = 0.0.55 • corr DXA femoral neck = 0.57 • corr DXA Wards = 0.52 • corr DXA trochanter = 0.55	
3. stiffness index	• CV(normals)=1.49% • CV(osteopenic)=1.46%	• corr DXA spine = 0.59 • corr DXA femoral neck = 0.67 • corr DXA Wards = 0.63 • corr DXA trochanter = 0.62	
Wendt 1996 (77) cross-sectional n=236		• US parameters in women with fractures was significantly lower than values in the controls	"At a BUA/SOS index of 68 the sensitivity = 85% and specificity = 77% for osteoporotic fractures"
Giorgino abs 1997 (83) case control, treatment with HRT			
stiffness index			• mean % Δ in treatment group = 5.3% over 3 yrs, in controls = -5.9% • 78% and 62% of treated and controls showed an SI Δ >precision error at 1 year.

•

Table 6: Lunar Achilles

Author	Precision	Predicting DXA	Predicting Fractures
Yamamoto 1997 (78) Japanese women cross-sectional (n=3212), subset for follow-up(n=199), subset for vertebral # prevalence(n=654), subset for vert # incidence(n=116)	• In cross-sectional study US parameters decreased with age. Significant decreases were noted in the early post-menopausal period. • Corr between SOS and BUA = 0.35	%Δ in calcaneal BMD in normals = 1.0 to -2.7, in osteoporotics =0.3 to 2.7	• All US parameters significantly lower in patients with prevalent vertebral fracture • US parameters not significantly different in patients with incident fractures
1. speed of sound	• %Δ in normals = -0.2 to -0.4 • %Δ in osteoporotic=0.1 to -0.2	corr between Δ in SOS and Δ in BMD cal = 0.25	
2. BUA	• %Δ in normals = -2.4 to -3.3 • %Δ in osteoporotic=-3.1 to -3.8	corr between Δ in BUA and Δ in BMD cal = 0.01	
3. stiffness index	• %Δ in normals =-2.2 to -6.3 • %Δ in osteoporotic=-1.3 to -5.0	corr between Δ in SI and Δ in BMD cal = 0.19	
Yamakazi 1994(79) Japanese women cross-sectional	• short term reproducibility • All parameters decreased sig in the early post-menopause years		All US parameters where significantly lower in patients with vert fracture as compared to normals
1. speed of sound	• CV = 0.2% - 0.7%	• corr with DXA spine = 0.769, DXA femoral neck = 0.731	
2. BUA	• CV = 0.4% - 1.4%	• corr with DXA spine = 0.721, DXA femoral neck = 0.704	
3. stiffness index	• CV = 0.2% - 0.9%	• corr with DXA spine = 0.797, DXA femoral neck = 0.767	
Yamazaki 1997 (84) longitudinal study n=480	• mean % change over 4 years and annual change in early post-menopause		
1. speed of sound	• -0.57%/ 4yrs • annual = -0.32%(slightly exceeded precision error)		
2. BUA	• -1.36% • annual = -1.05%(half the precision error)		
3. stiffness index	• -4.22% • annual = -2.42%(slightly exceeded precision error)		
Cunningham 1996 (10) cross-sectional			
1. speed of sound	• CV = 0.46%	• corr with DXA spine = 0.47 • corr with DXA femoral neck = 0.498	
2. BUA	• CV = 1.5%	• corr with DXA spine = 0.41 • corr with DXA femoral neck = 0.537	
3. stiffness index	• CV = 3.01%	• corr with DXA spine = 0.474 • corr with DXA femoral neck = 0.546	

Table 6: Lunar Achilles

Author	Precision	Predicting DXA	Predicting Fractures
Mautalen 1995 (44) case control			
1. speed of sound	• precision = 5m/second		
2. BUA	• precision = 2 dB/MHz		
3. stiffness index	• CV = 2.1%		

Notes:

"BUA measured by the Achilles differs from that measured by the Walker Sonix instrument as the latter determines BUA from a sequence of measurements at discrete frequencies whereas the Achilles determines BUA through the discrete Fourier transformation of a broad spectrum of frequencies" (38)

Stiffness index as reported for LUNAR machines has two methods of calculation

1. SI = (0.67 x BUA) + (0.28 x SOS) - 420
2. SI = ½ (nBUA + nSOS)

- where nBUA = (BUA-50)/75 x 100 and nSOS = (SOS - 1380)/180 x 100

Table 7: McCue Cuba Clinical

Author	Precision	Predicting DXA	Predicting Fractures
Martin 1996 (42) cross-sectional peri-menopausal			
speed of sound(?)	• short term CV = 1.4%	• corr DXA spine = 0.11, femoral neck = 0.14, trochanter= 0.16, ward's = 0.13 • predicts 30% of women with T score<-2 by DXA	
BUA	• short term CV = 3.8%	• corr DXA spine = 0.34, femoral neck = 0.32, trochanter = 0.34, ward's = 0.36 • predicts 50% of women with T <-2 by DXA	
Herd 1994 (26) cross-sectional, referred for DXA, pre and post-menopausal n=300		• US predicts osteopenia spine AUC 0.71-0.75 • US predicts osteopenia femoral neck AUC 0.64-0.72	
speed of sound		• corr DXA spine = 0.48, femoral neck = 0.45	
BUA		• corr DXA spine = 0.54, femoral neck = 0.52	
CAV (combined attenuation and speed)		• corr DXA spine = 0.52, femoral neck = 0.45	
Graafmans 1996 (19) cross-sectional mixed pop	based on normal volunteers	based on patients referred for assessment of osteoporosis	
speed of sound	• CV (over 1 day) = 1.4% • CV (over 3 months) = 1.3%	• corr DXA spine = 0.48, femoral neck = 0.38, trochanter = 0.37	median values significantly lower in group with fractures (mixed)
BUA	• CV (over 1 day) = 3.4% • CV (over 3 months) = 4.9%	• corr DXA spine = 0.57, femoral neck = 0.56, trochanter = 0.57	median values significantly lower in group with fractures (mixed)
Herd 1993 (27) cross-sectional, mixed group n=229 *CUBA Research model	based on normal volunteers over 1 hour		
heel velocity (vs bone velocity)	• CV = 1.04%		
BUA	• CV = 6.3%		
Arden 1996 (1) twin study			
velocity of sound	• CV = 0.44%		
BUA	• CV = 2.5%		
Miller 1993 (46) cross-sectional mixed women n=279			
bone velocity	• CV = 2.71%, sCV = 12.8%		
heel velocity (includes soft tissue)	• CV = 1.1% sCV = 12.8%		
time of flight (includes pads)	• CV = 0.7% sCV = 12.7%		
Pocock 1996 (51) cross-sectional mixed n=201		"the standard error calculations…are so large as to render quantitative ultrasound … useless in any one individual in predicting …bone mineral density"	
speed of sound		corr with DXA spine =0.3-0.41, DXA femoral neck =0.29-0.37, DXA ward's =0.27-0.32, DXA trochanter = 0.36	
BUA		corr with DXA spine = 0.35-0.48, DXA femoral neck = 0.44-0.57, DXA ward's = 0.4-0.59, DXA trochanter = 0.41-0.48	

Table 8: Hologic Sahara

Author	Accuracy And Precision	Predicting DXA	Predicting Fractures
Kolta 1997 (31) cross-sectional post-menopausal n=126	short term precision		mean values for all parameters lower in patients with fracture history
speed of sound	• CV = 0.18% • corr with Walker Sonix = 0.86		
BUA	• CV = 3.01% • use of different coupling gels led to significant changes in BUA • corr with Walker Sonix = 0.84		
QUI	• CV = 1.715		
Sowers 1997 (65) cross-sectional, pregnant	correlation between repeated measures (?interval)		
speed of sound	• corr = 0.959		
BUA	• corr = 0.902		
stiffness index	• corr = 0.961		
Baran, Greenspan, Kiel, Bouxsein (unpublished) Hologic info pack cross-sectional mixed n=247		corr with DXA calcaneus = 0.82-0.85	
Hologic reference data study (unpublished) n=2208	• no data reported on precision and accuracy.		

References

1. Arden NK, Baker J, Hogg C, et al.. The heritability of bone mineral density, ultrasound of the calcaneus and hip axis length: a study of postmenopausal twins. *Journal of Bone & Mineral Research* 1996;11(4):530-4.

2. Avecilla L, Faulkner K. Clinical Acceptability of ultrsonometry. [Abstract] *Journal of Bone & Mineral Research* 1997;12:(Sup1)S385

3. Baran DT, Kelly AM, Karellas A, et al.. Ultrasound attenuation of the os calcis in women with osteoporosis and hip fractures. *Calcified Tissue International* 1988;43:138-42.

4. Bauer DC, Gluer CC, Cauley JA, et al.. Broadband ultrasound attenuation predicts fractures strongly and independently of densitometry in older women. A prospective study. Study of Osteoporotic Fractures Research Group. *Archives of Internal Medicine* 1997;157(6):629-34.

5. Bauer DC, Gluer CC, Genant HK, et al.. Quantitative ultrasound and vertebral fracture in postmenopausal women. Fracture Intervention Trial Research Group. *Journal of Bone & Mineral Research* 1995;10(3):353-8.

6. Blake GM, Gluer CC, Fogelman I. Bone densitometry: current status and future prospects. *British Journal of Radiology* 1997;70 Spec No:S177-S186

7. Bouxsein ML, Radloff SE. Quantitative ultrasound of the calcaneus reflects the mechanical properties of calcaneal trabecular bone. *Journal of Bone & Mineral Research* 1997;12(5):839-46.

8. Brooke-Wavell K, Jones PR, Pye DW. Ultrasound and dual X-ray absorptiometry measurement of the calcaneus: influence of region of interest location. *Calcified Tissue International* 1995;57(1):20-4.

9. Chow YW, Inman C, Pollintine P, et al.. Ultrasound bone densitometry and dual energy X-ray absorptiometry in patients with spinal cord injury: a cross-sectional study. *Spinal Cord* 1996;34(12):736-41.

10. Cunningham JL, Fordham JN, Hewitt TA, et al.. Ultrasound velocity and attenuation at different skeletal sites compared with bone mineral density measured using dual energy X-ray absorptiometry. *British Journal of Radiology* 1996;69(817):25-32.

11. Dretakis E, Damilakis J, Kontakis G, et al.. Variation between os calces as measured by broadband ultrasound attenuation. *British Journal of Radiology* 1994;67(799):636-8.

12. Dretakis EC, Kontakis GM, Steriopoulos CA, et al.. Decreased broadband ultrasound attenuation of the calcaneus in women with fragility fracture. 85 Colles' and hip

fracture cases versus 77 normal women. *Acta Orthopaedica Scandinavica* 1994;65(3):305-8.

13. Dretakis EK, Kontakis GM, Steriopoulos K, et al.. Broadband ultrasound attenuation of the os calcis in female postmenopausal patients with cervical and trochanteric fracture. *Calcified Tissue International* 1995;57(6):419-21.

14. Evans WD, Jones EA, Owen GM. Factors affecting the in vivo precision of broad-band ultrasonic attenuation. *Physics in Medicine & Biology* 1995;40(1):137-51.

15. Faulkner KG, McClung MR, Coleman LJ, et al.. Quantitative ultrasound of the heel: correlation with densitometric measurements at different skeletal sites. *Osteoporosis International* 1994;4(1):42-7.

16. Fuerst T, Schott AM, Meunier PJ. Quantitative ultrasound. *European Journal of Radiology* 1995;20:188-92.

17. Gluer CC, Cummings SR, Bauer DC, et al.. Osteoporosis: association of recent fractures with quantitative US findings. *Radiology* 1996;199(3):725-32.

18. Gonnelli S, Cepollaro C, Agnusdei D, et al.. Diagnostic value of ultrasound analysis and bone densitometry as predictors of vertebral deformity in postmenopausal women. *Osteoporosis International* 1995;5(6):413-8.

19. Graafmans WC, Van Lingen A, Ooms ME, et al.. Ultrasound measurements in the calcaneus: precision and its relation with bone mineral density of the heel, hip, and lumbar spine. *Bone* 1996;19(2):97-100.

20. Greenspan SL, Bouxsein ML, Melton ME, et al.. Precision and discriminatory ability of calcaneal bone assessment technologies. *Journal of Bone & Mineral Research* 1997;12(8):1303-13.

21. Hailey, D. *INAHTA project on the effectiveness of bone density measurement and associated treatments for prevention of fracture Background paper one. Methods used in the measurement of bone density.* Edmonton, Alberta Heritage Foundation for Medical Research, July 1996

22. Hans D, Arlot ME, Schott AM, et al.. Do ultrasound measurements on the os calcis reflect more the bone microarchitecture than the bone mass?: a two-dimensional histomorphometric study. *Bone* 1995;16(3):295-300.

23. Hans D, Dargent-Molina P, Schott AM, et al.. Ultrasonographic heel measurements to predict hip fracture in elderly women: the EPIDOS prospective study. *Lancet* 1996;348(9026):511-4.
24. Hans D, Schott AM, Arlot ME, et al.. Influence of anthropometric parameters on ultrasound measurements of Os calcis. *Osteoporosis International* 1995;5(5):371-6.

25. Hans D, Schott AM, Chapuy MC, et al.. Ultrasound measurements on the os calcis in a prospective multicenter study. *Calcified Tissue International* 1994;55(2):94-9.

26. Herd RJ, Blake GM, Miller CG, et al.. The ultrasonic assessment of osteopenia as defined by dual X-ray absorptiometry. *British Journal of Radiology* 1994;67(799):631-5.

27. Herd RJ, Blake GM, Ramalingam T, et al.. Measurements of postmenopausal bone loss with a new contact ultrasound system. *Calcified Tissue International* 1993;53(3):153-7.

28. Herd RJM, Ramalingham T, Ryan PJ, et al.. Measurements of broadband ultrasound attenuation in the calcaneus in premenopausal and postmenopausal women. *Osteoporosis International* 1992;2:247-51.

29. Howard GM, Nguyen TV, Pocock NA, et al.. Influence of handedness on calcaneal ultrasound: implications for assessment of osteoporosis and study design. *Osteoporosis International* 1997;7(3):190-4.

30. Johansen A, Stone MD. The effect of ankle oedema on bone ultrasound assessment at the heel. *Osteoporosis International* 1997;7(1):44-7.

31. Kolta S, Fechtenbaum J, Roux C. Bone assessment using a contact ultrasound system. [Abstract] *Journal of Bone & Mineral Research* 1997;12:(Sup 1)S386

32. Kolthoff N, Eiken P, Barenholdt O, et al.. Ultrasound measurements of the os calcis. Side differences and prediction of bone density in 39 persons. *Acta Orthopaedica Scandinavica* 1995;66(3):278-82.

33. Kotzki PO, Buyck D, Hans D, et al.. Influence of fat on ultrasound measurements of the os calcis. *Calcified Tissue International* 1994;54(2):91-5.

34. Krieg MA, Thiebaud D, Burckhardt P. Quantitative ultrasound of bone in institutionalized elderly women: a cross-sectional and longitudinal study. *Osteoporosis International* 1996;6(3):189-95.

35. Kroger H, Jurvelin J, Arnala I, et al.. Ultrasound attenuation of the calcaneus in normal subjects and in patients with wrist fracture. *Acta Orthopaedica Scandinavica* 1995;66(1):47-52.

36. Langton CM, Ballard PA, Bennett DK, et al.. A comparison of the sensitivity and specificity of calcaneal ultrasound measurements with clinical criteria for bone densitometry (DXA) referral. *Clinical Rheumatology* 1997;16(1):117-8.

37. Langton CM, Ballard PA, Langton DK, et al.. Maximising the cost effectiveness of BMD referral for DXA using ultrasound as a selective population pre-screen. *Technology & Health Care* 1997;5(3):235-41.

38. Lees B, Stevenson JC. Preliminary evaluation of a new ultrasound bone densitometer. *Calcified Tissue International* 1993;53(3):149-52.

39. Machado A, Hannon R, Henry Y, et al.. Standardised coefficient of variation for dual energy xray absorptiometry (DXA), quantitative ultrasound (QUS) and markers of bone turnover. *Journal of Bone & Mineral Research* 1997;12:(Supp 1)S258

40. Marshall D, Hailey D, Jonsson E. Health policy on bone density measurement technology in Sweden and Australia. *Health Policy* 1996;35:217-28.

41. Marshall D, Johnell O, Wedel H. Meta-analysis of how well measures of bone mineral density predict occurance of osteoporotic fractures. *British Medical Journal* 1996;312:1254-9.

42. Martin JC, Reid DM. Appendicular measurements in screening women for low axial bone mineral density. *British Journal of Radiology* 1996;69(819):234-40.

43. Massie A, Reid DM, Porter RW. Screening for osteoporosis: comparison between dual energy X-ray absorptiometry and broadband ultrasound attenuation in 1000 perimenopausal women. *Osteoporosis International* 1993;3(2):107-10.

44. Mautalen C, Vega E, Gonzalez D, et al.. Ultrasound and dual X-ray absorptiometry densitometry in women with hip fracture. *Calcified Tissue International* 1995;57(3):165-8.

45. McCloskey EV, Murray SA, Charlesworth D, et al.. Assessment of broadband ultrasound attenuation in the os calcis *in vitro. Clinical Science* 1990;78:221-5.

46. Miller CG, Herd RJM, Ramalingam T, et al.. Ultrasonic velocity measurements through the calcaneus: Which velocity should be measured? *Osteoporosis International* 1993;3(1):31-5.

47. Moris M, Peretz A, Tjeka R, et al.. Quantitative ultrasound bone measurements: normal values and comparison with bone mineral density by dual X-ray absorptiometry. *Calcified Tissue International* 1995;57(1):6-10.

48. Morris R, Mazess R, Trempe J, et al.. Stiffness index compensates for temperature variation in ultrasound densitomet.ry. *Journal of Bone & Mineral Research* 1997;12:(Sup1)S388

49. Naessen T, Mallmin H, Ljunghall S. Heel ultrasound in women after long-term ERT compared with bone densities in the forearm, spine and hip. *Osteoporosis International* 1995;5(3):205-10.

50. Pluijm SMF, Graafmans WC, Bouter LM, et al.. Ultrasound measurements for the prediction of osteoporotic fractures in elderly people. [Abstract] *Journal of Bone & Mineral Research* 1997;12:(Sup1)S362

51. Pocock NA, Noakes KA, Howard GM, et al.. Screening for osteoporosis: what is the role of heel ultrasound? *Medical Journal of Australia* 1996;164(6):367-70.

52. Poet JL, Serabian IT, Camboulives H, et al.. Broadband ultrasound attenuation of the os calcis: preliminary study. *Clinical Rheumatology* 1994;13(2):234-8.

53. Porter RW, Miller CG, Grainger D, et al.. Prediction of hip fracture in elderly women: a prospective study. *British Journal of Medicine* 1990;301:638-41.

54. Rosenthall L. Selective supplementation of calcaneal ultrasound densitometry with dual-energy x-ray absorptiometry of the spine and femur for population screening. *Canadian Association of Radiologists Journal* 1997;48(1):38-41.

55. Rosenthall L. Influence of bone quality on precision of calcaneal ultrasonometry. *Calcified Tissue International* 1997;61(2):139-41.

56. Rosenthall L, Caminis J, Tenenhouse A. Correlation of ultrasound velocity in the tibial cortex, calcaneal ultrasonography, and bone mineral densitometry of the spine and femur. *Calcified Tissue International* 1996;58(6):415-8.

57. Rosenthall L, Tenenhouse A, Caminis J. A correlative study of ultrasound calcaneal and dual-energy X-ray absorptiometry bone measurements of the lumbar spine and femur in 1000 women. *European Journal of Nuclear Medicine* 1995;22(5):402-6.

58. Ross P, Huang C, Davis J, et al.. Predicting vertebral deformity using bone densitometry at various skeletal sites and calcaneus ultrasound. *Bone* 1995;16(3):325-32.

59. Roux C, Lemonnier E, Kolta S, et al.. Broadband ultrasound attenuation of the calcaneus and bone density measurements. *Revue du Rhumatisme (English Edition)* 1993;60(12):771-80.

60. Sakata S, Kushida K, Yamazaki K, et al.. Ultrasound bone densitometry of os calcis in elderly Japanese women with hip fracture. *Calcified Tissue International* 1997;60(1):2-7.

61. Salamone LM, Krall EA, Harris S, et al.. Comparison of broadband ultrasound attenuation to single X-ray absorptiometry measurements at the calcaneus in postmenopausal women. *Calcified Tissue International* 1994;54(2):87-90.

62. Schott AM, Hans D, Garnero P, et al.. Age-related changes in Os calcis ultrasonic indices: a 2-year prospective study. *Osteoporosis International* 1995;5(6):478-83.

63. Schott AM, Hans D, Sornay-Rendu E, et al.. Ultrasound measurements on os calcis: precision and age-related changes in a normal female population. *Osteoporosis International* 1993;3(5):249-54.

64. Schott AM, Weill-Engerer S, Hans D, et al.. Ultrasound discriminates patients with hip fracture equally well as dual energy x-ray absorptiometry and independently of bone mineral density. *Journal of Bone & Mineral Research* 1995;10:243-9.

65. Sowers M, Jannausch M, Schall T, et al.. Reproducibility of ultrasound instrument to assess bone status in pregnant women. [Abstract] *Journal of Bone & Mineral Research* 1997;12:(Sup 1)S388

66. Stewart A, Felsenberg D, Kalidis L, et al.. Vertebral fractures in men and women: How discriminative are bone mass measurements? *British Journal of Radiology* 1995;68(810):614-20.

67. Stewart A, Reid DM, Porter RW. Broadband ultrasound attenuation and dual energy X-ray absorptiometry in patients with hip fractures: Which technique discriminates fracture risk. *Calcified Tissue International* 1994;54(6):466-9.

68. Stewart A, Torgerson DJ, Reid DM. Prediction of fractures in perimenopausal women: a comparison of dual energy x ray absorptiometry and broadband ultrasound attenuation. *Annals of the Rheumatic Diseases* 1996;55(2):140-2.

69. Strelitzki R, Clarke AJ, Truscott JG, et al.. Ultrasonic measurement: an evaluation of three heel bone scanners compared with a bench-top system. *Osteoporosis International* 1996;6(6):471-9.

70. Suarez-Almazor M, Homik JE, Messina D, et al.. The attitudes and beliefs of family physicians and gynecologists in relation to the prevention and treatment of osteoporosis. *Journal of Bone & Mineral Research* 1997;12:1100-7.

71. Thompson P, Taylor J, Fisher A. A prospective study of fracture prediction using heel ultrasound in postmenopausal women. [Abstract] *Journal of Bone & Mineral Research* 1996;11:(11)1829

72. Turner CH, Peacock M, Timmerman L, et al.. Calcaneal ultrasonic measurements discriminate hip fracture independently of bone mass. *Osteoporosis International* 1995;5(2):130-5.

73. Vahlensieck M, Gluer CC, Engelke K, et al.. [Osteoporosis diagnosis by broad-band ultrasound attenuation (BUA): its correlation with established measurement procedures of bone densitometry]. [German]. *Rofo Fortschritte auf dem Gebiete der Rontgenstrahlen und der Neuen Bildgebenden Verfahren* 1993;158(5):479-82.

74. van Daele PL, Burger H, Algra D, et al.. Age-associated changes in ultrasound measurements of the calcaneus in men and women: the Rotterdam Study. *Journal of Bone & Mineral Research* 1994;9(11):1751-7.

75. van Daele PL, Burger H, De Laet CE, et al.. Longitudinal changes in ultrasound parameters of the calcaneus. *Osteoporosis International* 1997;7(3):207-12.

76. Webber CE. Uncertainties in bone mineral density T scores. *Clinics in Investigational Medicine* 1998;21(2):88-96.

77. Wendt B, Cornelius A, Otto R. [Diagnosis of osteoporosis with ultrasound densitometry of the calcaneus]. [German]. *Radiologe* 1996;36(1):58-63.

78. Yamamoto A, Kishimoto H, Katagiri H. Clinical and experimental studies of quantitative ultrasound measurement in the os calcis: Prevalence and incidence of vertebral fracture. *Journal of Orthopaedic Science* 1997;2(2):64-74.

79. Yamazaki K, Kushida K, Ohmura A, et al.. Ultrasound bone densitometry of the os calcis in Japanese women. *Osteoporosis International* 1994;4(4):220-5.

80. Young H, Howey S, Purdie DW. Broadband ultrasound attenuation compared with dual-energy X-ray absorptiometry in screening for postmenopausal low bone density. *Osteoporosis International* 1993;3(3):160

81. Jovell AJ, Navarro-Rubio MD. Evaluacion de la evidencia cientifica. *Medicina Clinica* 1995; 105: 740-43.

82. Giorgino R, Paparella P, Lorusso D, et al. The effects of two different regimens of intramuscular clondronate on os calcis ultrasound densitometry: the results of a 2-year prospective study. *Journal of Bone and Mineral Research* 1997;12(supp): S475.

83. Giorgino R, Paparella P, Lorussoo D, et al. Longitudinal effects of three-year hormonal replacement therapy on quantitative ultrasound bone measurements. *Journal of Bone and Mineral Research* 1997;12(supp): S103.

84. Yamakazi K, Kushida K, Sakata S, et al. Menopause effects on ultrasound variables in a population based-longitudinal study. *Journal of Bone and Mineral Research* 1997;12(supp): S176.