Position Statement

Quantitative Ultrasound in the Management of Osteoporosis: The 2007 ISCD Official Positions

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Abstract

Dual-energy X-ray absorptiometry (DXA) is commonly used in the care of patients for diagnostic classification of osteoporosis, low bone mass (osteopenia), or normal bone density; assessment of fracture risk; and monitoring changes in bone density over time. The development of other technologies for the evaluation of skeletal health has been associated with uncertainties regarding their applications in clinical practice. Quantitative ultrasound (QUS), a technology for measuring properties of bone at peripheral skeletal sites, is more portable and less expensive than DXA, without the use of ionizing radiation. The proliferation of QUS devices that are technologically diverse, measuring and reporting variable bone parameters in different ways, examining different skeletal sites, and having differing levels of validating data for association with DXA-measured bone density and fracture risk, has created many challenges in applying QUS for use in clinical practice. The International Society for Clinical Densitometry (ISCD) 2007 Position Development Conference (PDC) addressed clinical applications of QUS for fracture risk assessment, diagnosis of osteoporosis, treatment initiation, monitoring of treatment, and quality assurance/quality control. The ISCD Official Positions on QUS resulting from this PDC, the rationale for their establishment, and recommendations for further study are presented here.

Key Words: Diagnosis; fracture; guidelines; osteoporosis; QUS; recommendations; standards; treatment; ultrasound.

Introduction

Osteoporosis is defined as a "disease characterized by low bone mass and microarchitectural deterioration of bone tissue

leading to enhanced bone fragility and a consequent increase in fracture risk" *(1)*. This definition does not provide explicit diagnostic criteria that allow one to determine whether an individual is osteoporotic or not. As there is no available clinical tool to assess bone microarchitecture or directly measure bone fragility, measurement of bone mineral density (BMD) assessed by dual-energy X-ray absorptiometry (DXA) is used to diagnose osteoporosis *(2)*. The World Health Organization (WHO) proposed a set of operational criteria to define osteoporosis in postmenopausal Caucasian women *(3)*. The BMD value of an individual patient is expressed in terms of

the number of standard deviations from the mean BMD of a healthy young-adult reference population, commonly referred to as the T-score. Osteoporosis has been defined by a T-score of −2.5 or less. The WHO diagnostic criteria are applied to BMD measured at the spine, hip, or forearm *(4)*; however, the combination of socio-economical emphasis on hip fractures and studies showing that BMD measured at the proximal femur has the strongest association with hip fracture has served to focus some clinical treatment guidelines on BMD measurements assessed by DXA at the hip (femoral neck and/or total hip) *(5)*.

The proliferation of bone densitometers using different technologies for measuring different skeletal sites, along with the absence of technology-specific guidelines, has created great uncertainty in applying the results to managing the care of individual patients in clinical practice. Amongst the technologies, there is a growing interest in the use of quantitative ultrasound (QUS). QUS is inexpensive, transportable, ionizing radiation-free, and proven to predict hip fractures and all osteoporotic fractures in elderly women as well as central DXA *(6−8)*. For the last 15 yr, the body of evidence highlighting the ability of QUS to predict fracture risk is substantial, but its use in clinical practice is still not well defined. Uncertainties that include long term stability, cross-calibration, reference databases, precision issues, and technical diversity have limited its clinical application *(9,10)*.

The role of the ISCD QUS Task Force was to review the medical literature and propose a set of operational recommendations for the clinical use of QUS. Five major topics were scrutinized:

- QUS and fracture risk assessment
- QUS and diagnosis of osteoporosis
- QUS and treatment initiation
- QUS and treatment monitoring
- QUS and quality assurance/quality control (QA/QC)

Note: Current recommendations can only be applied to primary osteoporosis (i.e., postmenopausal and osteoporosis associated with aging). Subjects with secondary osteoporosis or metabolic bone disease (e.g. glucocorticoid-induced osteoporosis, hyperparathyroidism, osteomalacia) should be managed according to good medical practice.

Methodology

The methods used to develop, and grading system applied to the ISCD Official Positions, are presented in the Executive Summary that accompanies this paper. In brief, all Official Positions were rated by the Expert Panel in four categories: Quality of evidence (Good, Fair, Poor), where Good is evidence that includes results from well-designed, well-conducted studies in representative populations; Fair is evidence sufficient to determine effects on outcomes, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies; and Poor is evidence that is insufficient to assess the effects on outcomes because of limited number or power of studies, important flaws in

their design or conduct, or gaps in the chain of evidence or information.

Strength of the recommendation (A, B, or C), where A is a strong recommendation supported by the evidence; B is a recommendation supported by the evidence; and C is a recommendation supported primarily by expert opinion).

Applicability (worldwide = W or variable, according to local requirements = L), and Necessity, where "Necessary" indicates that the indication or procedure is necessary due to the health benefits outweighing the risk to such an extent that it must be offered to all patients and the magnitude of the expected benefit is not small.

Technological Diversity Amongst QUS Devices

ISCD Official Position

- For QUS, bone density measurements from different devices cannot be directly compared.
  Grade: Good-A-W-Necessary

Rationale

Ultrasounds are sound waves beyond the audible threshold, typically defined as 20 kilo hertz (kHz). The physical and mechanical properties of bone progressively alter the shape, intensity, and speed of the propagating wave. Bone tissue may therefore be characterized in terms of ultrasound velocity and attenuation: however, one must interpret these parameters with care, since there are differences in their calculation with different manufacturers and models. For example, velocity may be bone velocity; heel velocity; time of flight velocity; phase velocity; or amplitude dependent velocity. Similarly, ultrasound attenuation may use different algorithms which vary as a function of the frequencies of the device as well as the mathematical approach. For clarification and standardization purposes amongst the different heel QUS devices, the Expert Panel rated the following as appropriate terminology:

- Broadband Ultrasound Attenuation (BUA), in dB/MHz, is the recommended attenuation parameter.
- Speed of Sound (SOS), in meters per second (m/s), is the recommended velocity parameter.
- When available, a composite parameter combining BUA and SOS, such as Stiffness Index (SI), or Quantitative Ultrasound Index (QUI), may be clinically useful.

Detailed technical descriptions of the major QUS devices have been published elsewhere *(6,7,11)*. QUS instruments from different manufacturers have significant differences, particularly in their calibration methods; skeletal sites of measurement and analysis; acquisition technique; analysis software; and scanner designs.

Discussion

Technological diversities amongst QUS devices are not a new concept in the medical field. Indeed, while DXA is the gold standard for the diagnosis of osteoporosis, there are major differences among manufacturers and models. For example,

there may be single or multiple detectors. Dual X-ray may be generated by a filter or switching. Each manufacturer has its own BMD calculation algorithms (different bone edge detection, intra marrow fat correction, etc. As a result, absolute value of BMD, the common parameter for all DXA devices, cannot be compared with different manufacturers and models.

It is usual to categorize DXA into fan, pencil or cone beam X-ray devices. Similarly, taking into account the technical diversities, QUS devices may be classified into three groups according to the type of ultrasound transmission:

- Trabecular transverse transmission. The ultrasound waves travel through trabecular bone. Currently, this category of devices uses water-based or direct-contact systems at the heel. In the latter case, the coupling medium is oil-based gel and will be referred to as a dry system. The devices use focused or unfocussed transducers to acquire a set of parameters that may also include the formation of an ultrasound parametric image *(6,7)*.
- Cortical transverse transmission. The ultrasound waves travel through cortical bone. Currently, only phalanges contact devices fall into this category *(11)*.
- Cortical axial transmission. In this category of devices, the ultrasound waves are travelling along the bone. Ultrasound of the phalanges, radius, and tibia is currently under investigation. with such devices *(11)*.

The degree of technical diversity of QUS devices and parameters is much larger than what is commonly found in DXA. This increases the difficulties in comparing measurements with different QUS devices and may lead to misinterpretation of results. For example, precision may appear to be better for one device or parameter compared to another, when in fact the comparison is not valid. The biological variation and the mean of the considered parameter must be taken into account. One method of doing this is the use of standardized precision, which enables the comparison of different devices and parameters *(12,13)*.

To appreciate the complexity of such technical diversity amongst QUS devices and manufacturers, we have tabulated the following properties when available (Table1):

- The skeletal site assessed.
- The coupling agent (water or gel).
- The use of an image or not.
- The short-term precision (percentage coefficient of variation [CV%]), with the range of the value and the number of studies from which the values have been derived (in parenthesis). When no study showing CV% was found, then precision from the manufacturer was given with an ''m'' in parenthesis *(12)*.
- The standardized coefficient of variation (SCV%), using the following formula: root mean squared coefficient of variation (RMSCV) divided by (four times the standard deviations of the population divided by the mean of the population) *(13)*.
- The peak QUS values for Caucasian women extracted from multiple studies.

- The correlation with the corresponding parameters of the GE Lunar Achilles, which has been arbitrarily set as our ''reference device'', due to its use for most of the validation studies.

It becomes evident from Table 1, that direct comparison of the QUS devices cannot be performed without significant bias, i.e., results from one QUS device cannot be extrapolated to another one that is technologically different.

Additional Questions for Future Research

- For a given skeletal site, would there be additional value for standardization of the Region of Interest (ROI) as it is now for DXA?
- Does the QUS image improve overall clinical performance?
- Is there a need for new QUS parameters, e.g. Broadband Ultrasound Backscattered (BUB)?
- How can precision and long term stability of current QUS devices be improved?

Can QUS be Used for Fracture Risk Assessment?

ISCD Official Positions

- The only validated skeletal site for the clinical use of QUS in osteoporosis management is the heel.
  Grade: Good-A-W-Necessary
- Validated heel QUS devices predict fragility fracture in postmenopausal women (hip, vertebral and global fracture risk) and men over the age of 65 (hip and all non-vertebral fractures), independently of central DXA BMD.
  Grade: Good-A-W-Necessary
- Discordant results between heel QUS and central DXA are not infrequent and are not necessarily an indication of methodological error.
  Grade: Good-A-W-Necessary
- For QUS, different devices should be independently validated for fracture risk prediction by prospective trials or by demonstration of equivalence to a clinically validated device.
  Grade: Good-B-W-Necessary

Rationale

The clinical evidence that QUS of the heel by transverse transmission devices predicts fracture is stronger than for other QUS devices at other skeletal sites, e.g. cortical transverse transmission of the phalanges, or cortical axial transmission of the radius or phalange. Similarly, there are more data concerning hip and any fractures prediction compared to spine fractures. Overall, heel QUS can discriminate those with osteoporotic fractures (hip, spine, any osteoporotic fracture) from age-matched controls without osteoporotic fracture *(13−81)*. It is difficult to compare the performance of all the assessed devices due to differences in study design that include variation in inclusion/exclusion criteria and ethnicity

Table 1
Summary of Technical Specifications of Currently Available QUS Devices

Manufacturer	Model	Skeletal site	Coupling	Imaging	Parameter	PBM Caucasian women	Mean QUS, PM Caucasian women	CVmean: range (# studies)	SCV mean: range	R* (# studies)	Comments
GE—Lunar	Achilles +	Heel	Water	No	SOS	1567 ± 28.2	1521 ± 27	0.3: 0.2−0.5 (22)	4.2: 2.8−7.0	1	
	Achilles Exp.	Heel	Water/Gel	No	BUA	116 ± 9.4	106 ± 10	2.2: 0.9−4.4 (22)	5.8: 2.4−11.7	1	
	Achilles Ins.	Heel	Water/Gel	Yes	Stiffness	96 ± 14.5	76.9 ± 14	1.9: 0.6−3.0 (24)	2.6: 0.8−4.1	1	
Hologic	Sahara	Heel	Gel	No	SOS	1568 ± 27.6	1533 ± 27	0.3: 0.2−0.4 (6)	4.3: 2.9−5.7	0.86 (3)	
					BUA	75 ± 14.3	64.2 ± 15.0	4.1: 2.7−5.0 (6)	4.4: 2.9−5.4	0.77 (3)	
					QUI	103 ± 16.2	82.2 ± 16.7	2.6: 1.6−3.5 (4)	3.2: 2.0−4.3	0.87 (3)	
DMS	Ubis 3000/	Heel	Water	Yes	SOS	1521 ± 25.2	1499 ± 29	0.3: 0.2−0.3 (3)	3.9: 2.6−3.9	0.93 (2)	
	5000				BUA	68 ± 9.6	59.2 ± 14	2.2: 0.9−2.9 (3)	2.3: 1.0−3.1	0.87 (2)	
					STI			−	−		
Norland (McCue)	Cuba	Heel	Gel	No	VOS	−	−	0.6: 0.3−1.0 (4)	−	0.91 (1)	
	Clinical				BUA	89 ± 16.6	72.1 ± 15	3.4: 1.0−5.2 (6)	4.1: 1.2−6.3	0.87 (1)	
Quidel Inc.	QUS-2	Heel	Gel	No	BUA	89 ± 13.6	76.7 ± 17	3.0: 2.6−3.4 (2)	3.4: 2.9−3.9		
Meditech.	DTU-One	Heel	Water	Yes	SOS	1553 ± 9.3	1547 ± 11	0.2: 0.1−0.2 (4)	7.1: 3.6−7.1		
					BUA	50 ± 6.4	49.5 ± 7	2.6: 1.3−5.0 (5)	4.6: 2.3−8.8		
Aloka	AOS-100	Heel	Gel	No	SOS		1530 ± 24	0.2: 0.2−0.3 (1)	3.2: 3.2−7.8	0.89 (1)	
					IT		0.98 ± 0.08	1.4: 1.0−2.0 (1)	4.3: 3.1−6.1	0.77 (1)	
					OSI		2.27 ± 0.25	2.5: (1)	5.7	0.82 (1)	
Medilink	Osteospace	Heel	Gel	No	SOS			0.2 (m)			
					BUA			1.0 (m)			
					STI			−			
	Pecassus	Heel	Gel	No							
Ishikawa Seisakusho Ltd	Benus	Heel	Gel	No	SOS			1.0 (m)			
ELK Co.	CM-100/200	Heel	Gel	No	SOS			1.0 (m)			
Osteosys Co.	Sonost 2000	Heel	Water/Gel	No	SOS						Achilles like
	Sonost 3000		Gel		BUA						
					BQI						
BMtech21 Co.	OsteoImager Plus	Heel	Water	Yes	SOS						Ubis like
					BUA						
					OI						
	Osteo Pro	Heel	Oil	No	SOS			0.2 (m)			Achilles like
					BUA			0.2 (m)			
					OI			0.7 (m)			
IGEA	DBM Sonic 1200/BP	Phalanges	Gel	No	AD-SOS	2096 ± 72	1935 ± 85	1.0: 0.4−2.5 (9)	5.7: 2.3−14.2	0.34 (2)	
					UBPI		0.37 ± 0.19	1.9: 0.6−2.9 (3)	0.9: 0.3−1.4	−	
BeamMed (Sunlight)	Omnisense	Radius phalanges	Gel	No	SOS r	4133 ± 102	4034 ± 136	0.7: 0.2−1.0 (4)	5.2: 1.5−7.4	0.10 (2)	
					SOS p	4021 ± 176	3879 ± 190	0.8: 0.2−1.5 (4)	4.1: 1.0−7.7	0.10 (2)	

*Correlation to Achilles for matching parameters.

of subjects. To overcome these confounding factors, it would be necessary to include all the devices in the same study and have all the patients measured on all the machines. Few studies have performed such a comparison. A total of 11 relevant studies are summarized in Table 2.

The power of heel QUS to predict fracture observed in cross-sectional studies has been confirmed by many prospective studies, as shown in Table 3. The hazard ratio (HR, Cox regression), or relative risk (RR, logistic regression) per standard deviation decrease (HR/SD or RR/SD) for all ultrasound parameters is approximately 2.0 for the hip and spine *(82−92)*, and 1.5 for all fractures (Table 2) *(86,87,91−103)*. This is similar with results generally found using BMD assessed by DXA *(104,105)*. Moreover, the relationship found between QUS parameters and incident fractures was generally independent of the BMD assessed by DXA, whatever the skeletal site (site-matched or not) *(84,85,92,99,102)*. Discordant results between heel QUS and central DXA, which are not infrequent, are not necessarily an indication of methodological error but rather due to the independence between the two techniques. Heel QUS was also predictive of hip and non-vertebral fracture risk in men *(86,87,92,100)*, and in Asian subjects *(87,95)*. Only one study using UBA 575 did not show positive results in terms of hip fracture prediction *(106)*.

Since the level of evidence varies according to the manufacturer and the model of QUS device, results cannot be extrapolated from one device to another one that is technologically different. The best way to verify the ability of a technique to predict osteoporotic fracture would be to conduct prospective studies. However, the cost and logistics of such studies may be prohibitive for small companies. It is therefore helpful to use an approach called "equivalence studies." This approach must be used cautiously, as cross-sectional studies tend to systematically overestimate the odds ratio (OR) (compare Tables 2 and 3). According to this concept, if a prospective study is not available for a given device, an acceptable alternative with a compromised level of confidence is a population-based cross-sectional study with the following three performance characteristics (adapted from the National Osteoporosis Society *(107)*):

- High level of correlation (coefficient of correlation more than 0.8) with a well-established device (e.g. GE Lunar Achilles device)
- Good standardized precision (SCV within the 95% CI of the GE Lunar Achilles device for example).
- At least two independent cross-sectional studies per type of fracture (hip, vertebral and all fractures) showing significant discrimination between fractured and not fractured age matched controls.
  - Number of subjects (N) should be at least 70 per groups
  - Claims are fracture dependent.
  - One of the already established devices should be included in such studies for comparison.
  - No significance should be found when comparing the discriminative power of the devices using Areas Under the Receiver Operating Characteristic Curve (ROC).

The following Table 4 summarizes the ability of QUS devices for males and females to be considered as validated devices for fracture risk prediction.

Discussion

What has been demonstrated for heel-based devices does not apply to non-heel devices (cortical transverse and axial transmission devices), which in general show lower performance characteristics. Prospective data of the Osteoporosis and Ultrasound Study (OPUS) were presented during the 2007 meeting of the American Society for Bone and Mineral Research (ASBMR) *(108)*. Five QUS devices (four of the heel, one of the phalanges) were compared with DXA for the prediction of hip or vertebral fracture risk. The four heel QUS (Achilles+, DTU-one, QUS-2 and UBIS 5000) predicted hip and vertebral fractures at least as well as central DXA. The phalanges QUS DBM sonic failed to predict hip and vertebral fractures as already shown by others *(90,109)*. Only one prospective study assessed the ability of cortical axial transmission QUS to predict fracture in a population of elderly women living in nursing homes *(110)*. Whereas incident hip and non vertebral fracture risk was related to Achilles+ SI (HR 1.3 (1.1−1.4), respectively 1.1 (1.02−1.3)), Omnisense SOS phalange or radius was not predictive of fracture.

Figure 1 shows the results of 10 prospective studies that assessed the predictive power of heel QUS for hip, vertebral or non spine/clinical fractures in comparison with hip DXA (femoral neck or total hip BMD (HR/SD or RR/SD with 95% confidence intervals). The results of the OPUS study are included in this figure.

From a large body of evidence, validated heel QUS devices predict fragility fracture in postmenopausal women (hip, vertebral, and global fracture risk) and men over the age of 65 (hip and all non-vertebral fractures) independently, and as well as central DXA BMD.

Additional Questions for Future Research

- Would additional prospective studies for non-heel devices modify the current recommendations?
- How is it possible to reinforce the strength of evidence for the clinical use of QUS in non-Caucasian women and men?
- Considering the technical difficulties, what would be the additional value of measuring the hip by QUS?

Can QUS be Used to Diagnose Osteoporosis?

ISCD Official Position

- The WHO diagnostic classification cannot be applied to T-scores from measurements other than DXA at the femur neck, total femur, lumbar spine or one-third (33%) radius because those T-scores are not equivalent to T-scores derived by DXA.

  Grade: Good-A-W-Necessary

Table 2
Summary of the Major Cross-Sectional Studies Comparing Different QUS Devices

Reference	Mean age	Fractures	Fractured population	Compared population	Device	OR (95% CI)
Njeh et al. *(13)*	75	Hip	35	35	Achilles+ SI	2.8 (1.5−5.2)
					Sahara QUI	2.4 (1.3−4.3)
					AOS 100 OSI	2.4 (1.3−4.5)
					Cuba BUA	2.5 (1.2−5.1)
					UBIS 3000 BUA	3.4 (1.6−7.1)
					UBA 575+	2.5 (1.4−4.6)
					FN BMD	2.6 (1.3−5.1)
Eckmann et al. *(25)*	75	Hip	87	195	Achilles SI	3.1 (2.2−4.5)
					DBM 1200 SOS	1.0 (0.7−1.3)
					FN BMD	3.6 (2.4−5.5)
Eckmann et al. *(26)* (men)	75	Hip	31	68	Achilles SI	2.2 (1.2−3.9)
					DBM 1200 SOS	2.0 (1.2−3.3)
					FN BMD	4.8 (2.3−9.9)
Hans et al. *(45,46)*	77	Hip	50	46	Achilles+ SI	3.1 (1.6−6.2)
					Sahara QUI	2.3 (1.2−4.4)
					UBIS 5000 BUA	2.3 (1.2−4.3)
			38	38	Omnisens SOS rad	2.7 (1.4−5.3)
Krieg et al. *(55)*	75	Hip	86	3866	Achilles+ SI	2.7 (2.1−3.5)
					Sahara QUI	2.4 (1.8−3.2)
					DBM 1200 ADSOS	1.4 (1.1−1.7)
Frost et al. *(29)*	63	Vertebral	83	164	UBA 575 + BUA	3.2 (2.1−4.7)
					DTU-one BUA	3.3 (2.3−4.6)
					FN BMD	2.9 (1.9−4.4)
Glüer et al. *(34)*	55−79	Vertebral	379	1506	Achilles SI	1.5 (1.3−1.7)
				1943	DTU-one BUA	1.3 (1.2−1.4)
				1173	QUS-2 BUA	1.4 (1.2−1.6)
				1738	UBIS 5000 BUA	1.4 (1.2−1.6)
				1908	DBM BP SOS	1.2 (1.1−1.4)
				1961	Spine sBMD	1.6 (1.4−1.8)
				1995	TH sBMD	1.6 (1.4−1.8)
Clowes et al. *(19)*	68	Vertebral	73	501	Achilles BUA	3.1 (2.2−4.3)
					DTU-one BUA	3.2 (2.4−4.3)
					QUS-2 BUA	3.7 (2.6−5.2)
					UBIS 5000 BUA	4.0 (2.9−5.7)
					Omnisens SOS phal	1.3 (0.99−1.8)
					Omnisens SOS rad	1.5 (1.2−2.0)
					DBM BP SOS	1.6 (1.2−2.3)
					TH BMD	4.3 (3.0−6.2)
Hartl et al. *(47)*	70	Vertebral ≥ 2 fractures	19	396	Achilles+ SI	3.0 (1.6−5.6)
					Sahara QUI	3.8 (1.8−8.2)
					DBM PB SOS	2.1 (1.3−3.4)
					FN BMD	1.9 (1.2−3.9)
					LS BMD	2.1 (1.2−3.9)

(*Continued*)

Table 2 (Continued)

Reference	Mean age	Fractures	Fractured population	Compared population	Device	OR (95% CI)
Frost et al. *(30)*	62	Osteoporotic	154	221	Sahara eBMD	3.2 (2.3−4.3)
					DTU-one BUA	2.5 (1.9−3.3)
					FN BMD	2.2 (1.7−2.9)
Gonnelli et al. *(38)* (men)	60	Osteoporotic	133	268	Achilles+ SI	3.2 (2.3−4.5)
					DBM BP SOS	2.0 (1.3−2.8)
					FN BMD	3.2 (2.3−4.4)

Rationale

The WHO classification of BMD was established using central DXA technologies at specified skeletal sites with a female postmenopausal Caucasian reference database *(3)*. It is not possible to apply the WHO criteria to other technologies and other skeletal sites. The WHO T-score range of −2.5 or less identifies approximately 30% of postmenopausal women as having osteoporosis, which also approximates the average lifetime risk of osteoporotic fractures (clinical spine fracture, hip and forearm) *(1−3)*. The T-score diagnostic threshold of −2.5 cannot be applied to QUS devices without the risk of having discrepancies in the number of women diagnosed with osteoporosis. For example, if the prevalence of osteoporosis is defined as the population below a T-score threshold of −2.5, then several studies have shown that the prevalence varies widely (over 10-fold) when the same T-score is applied to different QUS devices and skeletal sites *(81,112−116)*. To illustrate this point, at 60 yr old, the prevalence of women below the T-score threshold of −2.5 is: 4% for Sahara QUI; 12% for Omnisense radius SOS; 16% for Achilles SI; 24% for Omnisense phalanges SOS; and 50% for DBM sonic ADSOS. Using DXA, the prevalence of women below the T-score −2.5 at the same age is: 12% for lumbar spine BMD; 14% for femoral neck BMD; and 7% for total hip BMD (*see* also Fig. 2). Unfortunately, it is not unusual to see physicians incorrectly apply the WHO criteria for diagnostic classification to QUS measurements for patients in clinical practice.

Discussion

Osteoporosis cannot be diagnosed by QUS according to the WHO classification. However, one could define specific thresholds to identify patients at high or low risk of having osteoporosis. This approach has been proposed by the UK National Osteoporosis Society for use with pDXA techniques *(117,118)* and others *(119,120)*. They have defined upper and lower values for pDXA parameters with 90% sensitivity (upper threshold) and 90% specificity (lower threshold) for identifying patients with central DXA T-score of −2.5 or lower at the hip or spine. At or above the threshold of 90% sensitivity, the likelihood of having osteoporosis was very low, with only 10% of subjects being rated as false-negative. On the other hand, a specificity of 90% could be used to define subjects as having high likelihood of osteoporosis. This leads to a low rate (10%) of false-positive subjects.

It could be appropriate to apply this concept to QUS, given the high correlation between QUS parameters and skeletal site-matched bone mass assessed by DXA/pDXA. To illustrate such an approach with QUS, we have calculated the upper and lower thresholds for Sahara and the Achilles devices from the data published by Hans et al. *(119,120)*. The upper thresholds for the QUI or Stiffness Index are 83 units and 78% for the Sahara and the Achilles respectively and the corresponding lower thresholds are 59 units and 57%. To estimate the performance of these thresholds, we applied the Achilles calculated thresholds in the 5954 women, aged 75 yr and older, included in the Epidemiology of Osteoporosis (EPIDOS) study who had an assessment of their femoral neck by DXA, and of their heel by Achilles QUS. In this example, the percentage of false positive was of 11%, whereas the percentage of false negative was of 13%. The outcomes are displayed in Figures 2 and 3.

For women with heel QUS parameters that lie between upper and lower thresholds, BMD measurement assessed by central DXA could be recommended. In our example, 56% of the women lie between the two thresholds. Among this group about half of them will be classified as osteoporotic at their femoral neck according to the WHO criteria. The overall prevalence of osteoporosis combining heel QUS and hip DXA was in the order of 55%, which corresponds to the prevalence of osteoporosis in our population using hip DXA alone (≤−2.5 T-score).

Discordant classification in the results between heel QUS and central DXA due to the partial independence between the two techniques should not undermine any of these techniques. Indeed, given the similar predictive power of DXA and QUS, a low result with one of the two techniques corresponds to a high risk of fracture.

Additional Question for Future Research

- Is there an added value to combining DXA and QUS measurements in the management of osteoporosis?

Can QUS be Used to Initiate Treatment?

ISCD Official Positions

- Central DXA measurements at the spine and femur are the preferred method for making therapeutic decisions

Table 3
Summary of the Prospective Studies for Hip, Vertebral, and all Fracture Prediction (Only If HR/RR Available)

	Mean age	Fractures	Fractured population	Compared population	Method	Adjustments	HR/RR (95% CI)	AUC	F-up, comments
Achilles, Achilles +/SI (BUA for ref. 85)									
Hans et al. (84)	80	Hip	115	5547	Cox per 1 SD	Age, weight, center	2.0 (1.6−2.4)		2 yr, BUA
Thompson et al. (96)	61	OPF	26	3000	Cox per 1 SD	Age	2.2 (1.4−3.4)		2 yr
Huopio et al. (99)	60	OPF	24	390	Cox per 1 SD	Age, weight, height, HRT, fracture, FN BMD	1.9 (1.3−2.9)		2.6 yr
Schott et al. (88)	80	Hip	192	5511	Cox per 1 SD	Age, weight, fracture	1.8 (1.6−2.1)		4 yr
Fujiwara et al. (87)	68	Hip	34	3812	Cox per 1 SD	Age, gender	3.1 (2.6−3.6)		5 yr, men & women Japanese
		NVF	216	3812			1.8 (1.6−2.0)		
Devine et al. (101)	75	Any	147	1161	Cox per 1 SD	Age, weight, HRT topic, treatment, fracture	1.4 (1.1−1.7)		3 yr
Gluer et al. (89)	65	Vertebral	17	107	LR per 1 SD	Age	2.4 (1.1−5.1)		1 yr, treated women
Krieg et al. (90)	75	Hip	80	6982	Cox per 1 SD	Age, BMI, center	2.6 (1.9−3.4)	0.72 (0.66−0.78)	3 yr
Pinheiro et al. (103)	75	OPF	41	167	Cox per 1 SD	Age, BMI, fracture, smoking, comorbidities, activity, drugs	2.2 (1.3−3.8)	0.78 (0.71−0.86)	5 yr
Krieg and Hans (111)	75	NVF	394	4534	Cox per 1 SD	Age, BMI, center	1.6 (1.5−1.8)	0.63 (0.60−0.66)	3 yr
Hartl et al. (109)	70	Vertebral	24	408	LR per 1 SD	Age, height	2.3 (1.4−3.8)	0.70 (0.61, 0.81)	3 yr
UBA 575, UBA 575 +/BUA									
Bauer et al. (85)	76	Hip	54	5714	Cox per 1 SD	Age, center	2.0 (1.5−2.7)		2 yr
		NVF	350	5714			1.3 (1.2−1.5)		
Huang et al. (95)	74	Clinical	66	494	Cox per 1 SD	Age	1.7 (1.3−2.3)		2.7 yr
McGrother et al. (106)	78	Hip	37	1252	Cox per 1 SD	Age	1.1 (0.8−1.6)		3 yr
Stewart et al. (102)	49	OPF	31	730	Cox per 1 SD	Age, Weight, Height, Menopause	2.3 (1.5−3.3)	0.72 (0.69−0.75)	10 yr
Sahara/QUI									
Miller et al. (98)	50+	OPF	121	7441	Cox per 1 SD	Age, fracture	1.6 (1.3−1.9)	0.663	1 yr
Krieg et al. (90)	75	Hip	80	6982	Cox per 1 SD	Age, BMI, center	2.4 (1.8−3.2)	0.73 (0.67−0.79)	3 yr
Diez-Perez et al. (91)	72	Hip	49	5152	Cox per 1 SD	Age, fall, fracture, family, calcium intake	1.4 (1.0−2.0)	0.69 (0.04)	3 yr
Bauer et al. (92)	74	Hip	49	5557	Cox per 1 SD	Age, center	2.2 (1.6−3.1)		4.2 yr, men
		NVF	239	5342			1.6 (1.4−1.9)		
Diez-Perez et al. (91)	72	NVF	311	4890	Cox per 1 SD	Age, fall, fracture, family, calcium intake	1.3 (1.2−1.5)	0.67 (0.02)	3 yr
Krieg et al. (111)	75	NVF	394	4534	Cox per 1 SD	Age, BMI, center	1.7 (1.5−1.9)	0.64 (0.61−0.66)	3 yr
Hartl et al. (109)	70	Vertebral	24	408	LR per 1 SD	Age, height	2.8 (1.5−5.0)	0.72 (0.63, 0.82)	3 yr

Reference		Outcome		N	Method	Adjustments	RR (95% CI)	Follow-up
Cuba Clinical/BUA								
Pluijm et al. (109)	83	Hip	31	704	Cox per 1 SD	Age, gender	2.3 (1.4−3.7)	2.8 yrs, men & women, homes
Khaw et al. (100)	59	NVF	31	704	Cox per 20 dB/MHz	Age, weight, height, fracture, smoking	1.6 (1.2−2.1)	1.9 yr
		OPF	88	8240			1.9 (1.4−2.7)	
Khaw et al. (100)	59	OPF	33	6471	Cox per 20 dB/MHz	Age, weight, height, fracture, smoking	1.9 (1.3−2.9)	1.9 yr, men
DBM sonic 1200, DBM BP/AD-SOS								
Mele et al. (94)	53	Clinical	8	203	Cox per 1 SD	Age	1.3 (0.95−3.4)	3.2 yr
Krieg et al. (90)	75	Hip	80	6982	Cox per 1 SD	Age, BMI, center	1.2 (0.9−1.5)	3 yr
Krieg et al. (111)	75	NVF	394	4534	Cox per 1 SD	Age, BMI, center	1.3 (1.2−1.5)	3 yr
Hartl et al. (109)	70	Vertebral	24	408	LR per 1 SD	Age, height	1.1 (0.7−1.7)	3 yr

and should be used if possible. However, if central DXA cannot be done, pharmacologic treatment can be initiated if the fracture probability, as assessed by heel QUS using device specific thresholds and in conjunction with clinical risk factors, is sufficiently high.

Grade: Fair-C-W-Necessary

• Heel QUS in conjunction with clinical risk factors can be used to identify a population at very low fracture probability in which no further diagnostic evaluation may be necessary.

Grade: Good-B-W-Necessary

Rationale

Most of current recommendations for treatment initiation are based on central DXA and are summarized in Table 5 (121−127):

In all current recommendations, the most common basis for treatment initiation is the presence of low BMD. However the National Osteoporosis Foundation also includes as an alternative to low BMD, the presence of low energy vertebral or hip fractures (121). This approach to treatment initiation has been reinforced by the newly published study on the efficacy of zoledronic acid, demonstrating a significant reduction of vertebral and all clinical osteoporotic fractures in patients with acute hip fracture independent of the level of BMD values (129).

Many studies have demonstrated that heel trabecular transmission QUS parameters are strongly correlated with BMD, with a correlation coefficient of about 0.9 for skeletal site-matched regions-of-interest (10,130−132). This suggests that appropriate thresholds for QUS could be potentially defined to match the BMD treatment initiation thresholds with a certain degree of confidence. However, available therapeutic intervention thresholds vary due to either the presence or absence of clinical risk factors (CRFs) for fracture or different CRFs being used as a function of the professional group that are suggesting the recommendations. It is generally accepted that the BMD threshold for initiating treatment is higher when CRFs are present.

It is well-established that the basic parameters associated with QUS measurement of bone, namely the SOS and BUA, are associated with overall bone strength. Bone strength is related to bone density, bone architecture (macro and micro) bone turnover, as well as the degree of bone mineralization (9,10,131,133−139). It is likely that these factors work together in an integrated way to maintain the overall quality and strength of bone to perform its function while preserving its integrity and its resistance to fractures (9,10,131,133−139). Heel trabecular transverse transmission parameters correlate with bone strength up to 70−80% (136,140−147).

A key clinical question is whether individuals identified by QUS as "high-risk" for fracture will benefit significantly by treatment with antiresorptive agents or other specific medications against osteoporosis. Currently, there are no randomized clinical trials showing reduction of fracture risk in patients selected for treatment according to QUS measurement. But we have to face a certain paradox: treatment with approved

Table 4
QUS and Fracture Prediction by Devices and by Types of Fractures

| | | | | Fracture risk assessment | |
| | | | | Female | Male |
Manufacturer	Model	Number of prospective studies	Level of confidence	H/V/ALL	H/V/ALL
GE—Lunar	Achilles	11	Very high	yes/yes/yes	yes/ukn/yes
Hologic	Sahara	5	High	yes/yes/yes	yes/ukn/yes
IGEA	DBM Sonic BP	5	High	no/no/yes	ukn/ukn/ukn
Norland (McCue)	Cuba Clinical	3	Medium	yes/ukn/yes	yes/ukn/yes
DMS	Ubis 3000/5000	1	Low	yes/yes/yes	ukn/ukn/ukn
Quidel Inc.	QUS-2	1	Low	yes/yes/yes	ukn/ukn/ukn
Meditech.	DTU-One	1	Low	yes/yes/yes	ukn/ukn/ukn
Medilink	Osteospace	0	absent	ukn/ukn/ukn	ukn/ukn/ukn
Aloka	AOS-100	0	absent	ukn/ukn/ukn	ukn/ukn/ukn
Ishikawa Seisakusho Ltd	Benus	0	absent	ukn/ukn/ukn	ukn/ukn/ukn
ELK Co.	CM-100/200	0	absent	ukn/ukn/ukn	ukn/ukn/ukn
Osteosys Co.	Sonost 2000/3000	0	absent	ukn/ukn/ukn	ukn/ukn/ukn
BMtech21 Co.	OsteoImager Plus	0	absent	ukn/ukn/ukn	ukn/ukn/ukn
	Osteo Pro	0	absent	ukn/ukn/ukn	ukn/ukn/ukn
BeamMed (Sunlight)	Omnisense	0	absent	ukn/ukn/ukn	ukn/ukn/ukn

Abbr: H, hip fractures; V, vertebral fractures; ALL, non vertebral fractures/clinical fractures; Ukn, unknown status—no available study published in peer reviewed journal.

antiresorptive drugs is associated with a reduction in fracture risk that is disproportionately greater than the increase in BMD, as determined by DXA. In other words, osteoporosis medications improve bone strength in ways that are not entirely dependent on BMD. Given the strong and positive relationship between trabecular transmission QUS parameters and bone strength, it is unlikely that bone strength will increase under treatment with decreasing QUS values.

Nevertheless, it is difficult to define a "high-risk" threshold that will identify a patient who is likely to benefit from
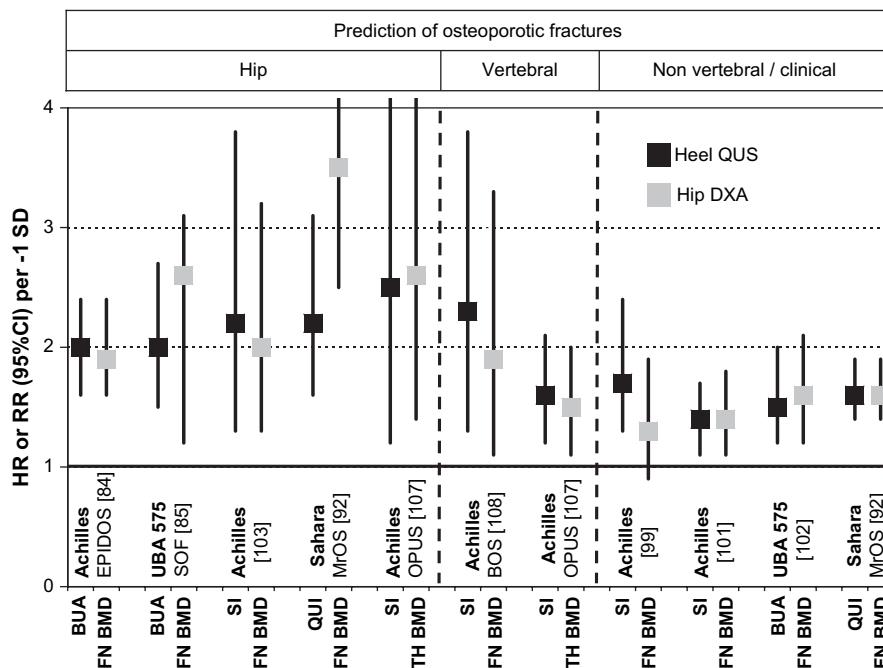

Fig. 1. Prospective studies comparing QUS with DXA for hip, vertebral and all osteoporotic fractures. Hazard ratios (HR) by Cox regression or relative risk (RR) by logistic regression per decrease of one SD of the different parameters.
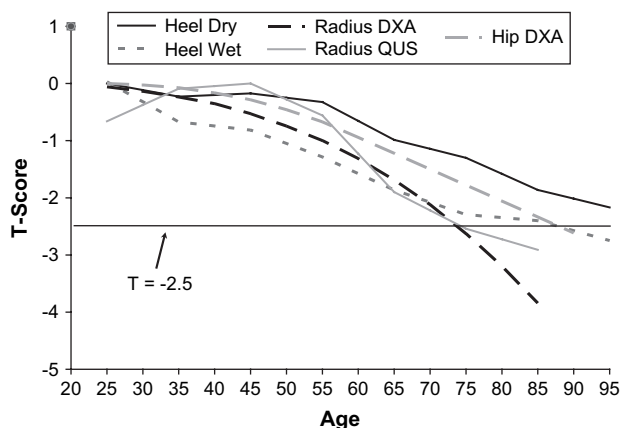
Fig. 2. Example of mean T-score as a function of age for several technologically different QUS and DXA devices (data from the manufacturer reference database).

osteoporotic medication with a sufficient level of confidence. This threshold would have to be device-specific based on DXA equivalence to the −2.5 T-score of the hip, and similar to the diagnostic lower threshold, as previously described.

Discussion

We recommend requiring the presence of major CRFs in conjunction with low QUS parameters to make treatment decisions. From meta-analyses and reviews published by Kanis *(148)* and Durosier *(105)* also involving QUS studies, we have identified the following CRFs to be used in the decision model: age over 75 yr *(149,150)*; low BMI (<20 kg/m²)

(149,151,152); previous fracture after age 50 yr *(149,152,153)*; maternal history of hip fracture *(154)*; current smoking *(155)*; diabetes mellitus *(152)*; ever use of glucocorticoids *(152,156)*; fall within the last 12 mo *(152,157)*; use of arms to stand up from a chair ("missed chair test") *(152,157,158)*.

The difficulty of applying CRFs to individual patients is the absence of quantitative values. Indeed, these parameters are usually categorical and the weight of each of them may vary. To overcome these difficulties, a task force of the WHO, lead by Kanis, is developing a 10-yr probability of osteoporotic fracture model combining femoral neck BMD and CRFs. Similarly, the calculation of an osteoporotic fracture probability taking into account the gradient of risk of QUS parameters and CRFs could replace a device-specific T-score. High- and low- risk probabilities then would help to determine the strategy for a given patient. This later model has been developed by Hans et al. based on more than 12000 Caucasian women *(159)*. It combines five CRFs in addition to age and Body Mass Index [*(1)* diabetes; *(2)* history of fracture; *(3)* history of a fall over the preceding 12 mo; *(4)* use arms to stand up from a chair; and *(5)* current cigarette smoking] and the heel stiffness index, as measured by QUS. Using this model, Hans et al. demonstrated that the probability of a fragility fracture for a given woman increases with the number of CRFs, and with a decreasing stiffness index (Fig. 4).

To convert this model into a useful clinical tool, risk thresholds must be defined based upon these probabilities. If we are using the same approach that was previously defined for the Achilles Stiffness Index (90% sensitivity and specificity), one could derive low- and high-risk probability of fracture thresholds (Fig. 5).

To display all the possible combinations between CRF, QUS and BMI, special software must be developed.
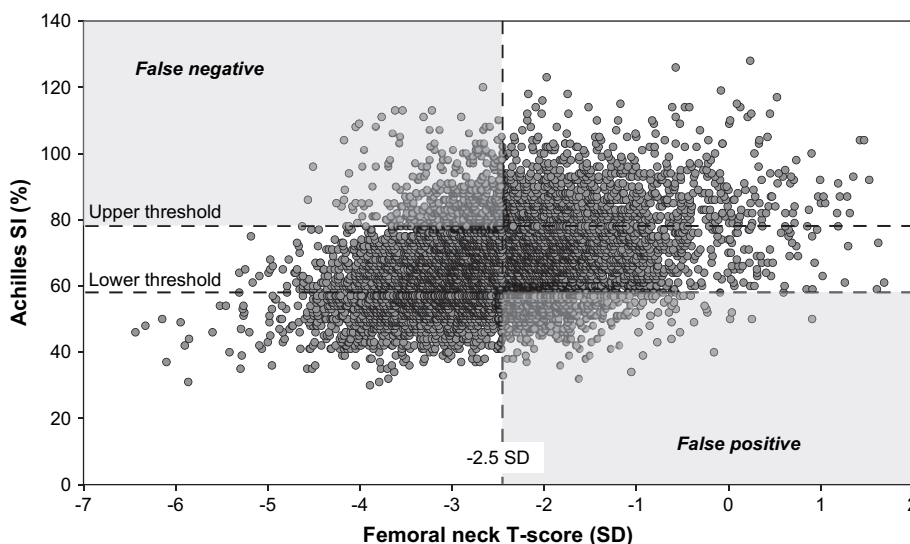

Fig. 3. Femoral neck T-score and Achilles SI in 5,954 elderly women (EPIDOS), and likelihood thresholds of having osteoporosis (SI 78% and 57%). Subjects above the upper threshold are at low risk (13% of false negative) whereas subjects below the lower threshold are at high risk (11% of false positive). DXA could be avoided in 44% of the population. The overall prevalence of osteoporosis combining heel QUS and hip DXA, or using hip DXA alone was the same (55%).

Table 5
Recommendations for Specific Anti-Fracture Therapy Initiation (2003 and after) OP TTT = Treatment of osteoporosis

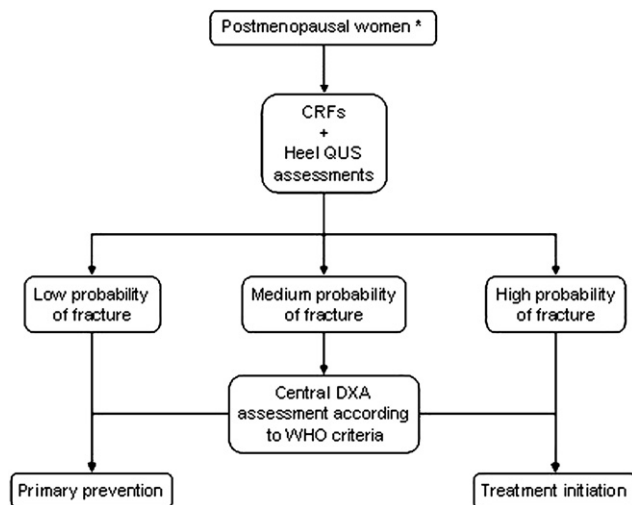|	OP TTT initiation, PM women	OP TTT initiation, Men 60+	Comments
NOF 2003 (USA) *(121)* & ACOG 2003 (USA) *(122)*	Prior vertebral (VF) or hip fracture (HF) T-score < −2.0 with no risk factors T-score < −1.5 with ≥ 1 risk factors		Major clinical risk factors (CRFs): low trauma peripheral fracture fragility fracture in a first degree relative weight < 127 lbs current smoking corticosteroids > 3 mo
AACE 2003 (USA) *(123)*	low-trauma fractures T-scores ≤ −2.5 with no risk factors T-score < −1.5 with ≥ 1 risk factors Women in whom non pharmacologic preventive measures are ineffective (bone loss continues or low trauma fractures occur)		
SIGN 2003 (UK) *(124)*	≥2 VF T-score < −2.5 ± FF	T-score < −2.5 ± FF	
NAMS 2006 (USA) *(125)*	Low trauma VF T-score ≤ −2.5 T-score ≤ −2 with RF		
DVO 2006 (Germany) *(126)*	VF & T-score < −2.0 10YR for VF + HF > 30% & T-score < −2.0 50−60: T-score −4.0 60−65: T-score −3.5 65−70: T-score −3.0 70−75: T-score −2.5 >75: T-score −2.0	VF & T-score < −2.0 10YR for VF + HF > 30% & T-score < −2.0 60−70: T-score − 4.0 70−75: T-score − 3.5 75−80: T-score − 3.0 80−85: T-score − 2.5 >85: T-score − 2.0	If clinical risk factor: +1 T-score HF in a parent low trauma peripheral fracture current smoking Multiple falls, immobility
AFSSAPS 2006 (France) *(128)*	T-score ≤ −2.5 & FF T-score < −1.0 & VF or HF T-score < −1.0 & other FF & CRFs T-score ≤ −2.5 & 60+ yr (T-score < −1.0 & major CRFs)		Clinical risk factors: corticosteroids family hip fracture low BMI current smoking increased risk of falls
OP Ca 2006 (Canada) *(127)*	50: LR > −2.3, MR: −2.3/−3.9, HR: <-3.9 55: LR > −1.9, MR: −1.9/−3.4, HR: <−3.4 60: LR > −1.4, MR: −1.4/−3.0, HR: <−3.0 65: LR > −1.0, MR: −1.0/−2.6, HR: <−2.6 70: LR > −0.8, MR: −0.8/−2.2, HR: <−2.2 75: LR > −0.7, MR: −0.7/−2.1, HR: <−2.1 80: LR > −0.6, MR: −0.6/−2.0, HR: <−2.0 85: LR > −0.7, MR: −0.7/−2.2, HR: <−2.2		If clinical risk factor: +1 category FF after 40 yr Corticosteroids

Abbr: PM, postmenopausal; VF, vertebral fracture; HF, hip fracture; FF, fragility fracture; 10YR, 10 yr risk; LR (<10%), low 10YR (hip, spine, forearm, proximal humerus); MR (10−20%), moderate 10YR; HR (>20%), high 10YR.

While the high correlation between QUS and BMD in trabecular bone has been confirmed (simulation studies *(160)*, in vitro studies *(161)*) and is relatively well understood, the situation with cortical bone is more complex. Many properties influence these measurements, including cortical thickness, mineralization, porosity, and lamellar structure, and it is not clear how much these properties contribute to bone strength *(162−165)*. There are interesting developments which might

lead to a separate assessment of factors related to bone strength, such as cortical thickness and material properties; however, this is not yet implemented in the two commercial devices (IGEA DBM Sonic and Beamed Omnisense devices). Given the minor performance of these non-heel methods, poor correlation to heel QUS or central BMD, and/or lack of data, we cannot currently recommend the use of these two devices for treatment initiation.

Example of a Case-Finding Strategy if DXA is not Available

* With no evidence for secondary osteoporosis or clinical evidence of vertebral fractures

Additional Questions for Future Research

- What would be the impact of the development of the 10- or 5-yr probability of fracture model taking into account QUS parameters and CRFs in the management of osteoporosis?
- How could optimal thresholds (high and low probability of fracture), taking into account cost-effectiveness considerations, be defined?
- How can randomized clinical trials be designed using low QUS values (or high probability of fracture) as inclusion criteria, in order to assess the possibility of using QUS/CRFs to make decisions on treatment initiation?
- How can QUS be used to optimize a case-finding strategy?

Can QUS be Used to Monitor Treatment?

ISCD Official Position

- QUS cannot be used to monitor the skeletal effects of treatments for osteoporosis.
  Good-A-W-Necessary

Rationale

At present, there are few studies evaluating the effects of pharmacological treatments on QUS parameters. Large randomized double-blind placebo-controlled studies are lacking. A summary of all studies involving treatment monitoring can be found in the Table 6, with no clear evidence that QUS is clinically useful in monitoring treatment *(166−182)*. Although QUS parameters at the heel and particularly the SI shows similar patterns with respect to axial BMD in osteoporosis patients treated with antiresorptive drugs in two studies, one in postmenopausal osteoporotic women *(168)*, the other in osteoporotic men *(167)*, the evidence is not strong enough to generalize the use of heel QUS for monitoring. Indeed, the number of subjects included in these studies remained too low and the designs are not based on double blind placebo control studies.

QUS parameters at the phalanges seem to be less sensitive than those at the heel in monitoring the effects of anti resorptive agents. This finding may be attributed to the low percentage of trabecular bone at this skeletal site, as well as it being a non-weight-bearing bone. Some of the data suggest that QUS parameters may have clinical utility in monitoring treatment with anabolic agents, but this needs confirmation by additional studies.

Discussion

The ability of QUS to monitor bone changes depends on the precision of QUS parameters and the magnitude of the response. From Table 1, we can see that in general, QUS is precise in the short-term, but the precision varies widely among devices and parameters being measured. In addition, when considering the Minimal Time Interval (MTI), it is clear that DXA offers greater clinical utility in terms of time to assess a significant change, compared to QUS.

For unclear reasons, current osteoporosis therapies are not always associated with measurable changes at peripheral skeletal sites depending on the region of interest and the device used. Whether this is a precision problem or simply a relative lack of treatment response at the peripheral site (or a combination of the two) remains unknown. In addition, the limited number and current design of studies could contribute to such unclear outcomes.

Additional Questions for Future Research

- Could large double-blind placebo-controlled studies for the treatment of osteoporosis use QUS for monitoring?
- Could QUS long-term precision be improved?
- Are there additional skeletal sites besides the heel that may be more responsive to treatment?

QUS Reporting

ISCD Official Positions

- For QUS, the report should combine the following standard elements:
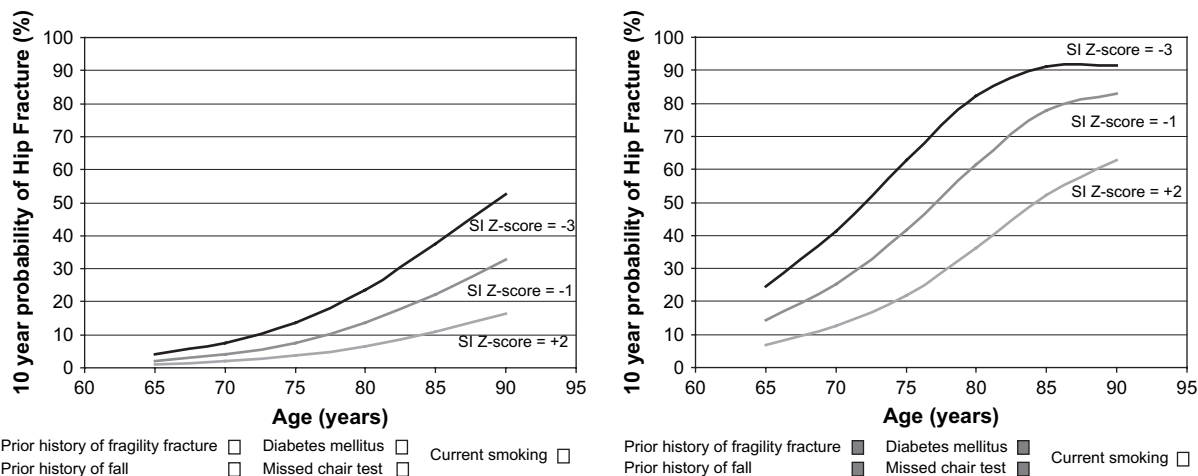 ○ Date of test

Fig. 4. Ten-yr probability of hip fracture for a given BMI of 26, at different Stiffness Index Z-score and the presence of no clinical risk factors (left side); or 4 clinical risk factors (i.e., prior history of fragility fracture, prior history of fall, diabetes mellitus and missed chair test) (right side). The shadowed squares mean the presence of this specific CRF.

○ Demographics (name, date of birth or age, sex)
○ Requesting provider
○ Names of those receiving copy of report
○ Indications for test
○ Manufacturer, and model of instrument and software version
○ Measurement value(s)
○ Reference database
○ Skeletal site/region of interest
○ Quality of test
○ Limitations of the test including a statement that the WHO diagnostic classification cannot be applied to T-scores obtained from QCT, pQCT, QUS, and pDXA (other than one-third (33%) radius) measurements
○ Clinical risk factors
○ Fracture risk estimation

Fig. 5. Example of hip fracture probabilities corresponding to low (dashed lines) and high (black) risk thresholds by age, for women with a BMI of 26, using a 10-yr hip fracture probability model, based upon QUS and CRFs, in the case where no CRFs have been identified.

○ A general statement that a medical evaluation for secondary causes of low BMD may be appropriate
○ Recommendations for follow-up imaging
   Grade: Fair-C-W-Necessary

• For QUS, the report may include the following optional item:
   ○ Recommendations for follow-up imaging Recommendations for pharmacological and non pharmacological interventions.
      Grade: Fair-C-W

Rationale

An appropriate QUS report should include information that identifies the patient, conveys the validity of the study, and provides clear exam interpretation and recommendations where appropriate. In addition, clear rationale of what should be included into a DXA report has been nicely described in a previous ISCD Position PDC publication *(184)*. Since a QUS device is a bone measurement tool that may be used in the management of osteoporosis, reporting should be as consistent as possible with DXA reporting. However, some reporting information must be adapted to the QUS technologies (e.g. limitation of the WHO classification).

Discussion

Information required for DXA examinations is relatively similar to that needed for QUS examinations, with some exceptions. The two exceptions found between the DXA and QUS reporting are related to:

Factors affecting Study Quality (see also the QA/QC section)

Factors influencing QUS measurements are usually different than those influencing DXA. For example, while
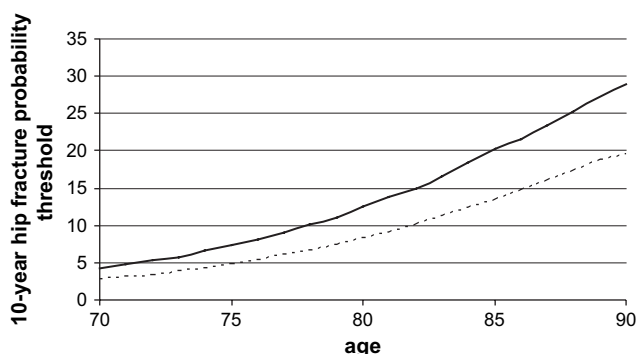
temperature can greatly impact SOS measurement, it does not affect BMD. Another example is the presence of edema at the heel, which also would negatively influence the QUS measurement but not DXA of the hip or spine.

Interpretation/limitations (see current PDC questions)

While the interpretation of DXA measurement is very much established, it is not obvious yet for QUS measurements. It is in the area of interpretation that both the greatest controversy and the greatest opportunity for explaining the results of bone testing exist. For example, the WHO diagnostic classification cannot be applied to T-scores obtained from QUS measurements. However, alternative interpretation would need to be discussed as highlighted at the 2007 PDC.

Additional Questions for Future Research

- How can QUS parameters and CRFs be quantitatively combined in a report?
- Can intervention thresholds be identified and reported using QUS?

What are the Quality Assurance and Quality Control (QA/QC) Criteria for QUS?

ISCD Official Positions

- For QUS, device-specific education and training should be given to the operators and interpreters prior to clinical use.
  Grade: Good-A-W-Necessary
- Quality control procedures should be performed regularly.
  Grade: Good-A-W-Necessary

Rationale

As a quantitative measurement, bone densitometry, including X-ray and QUS approaches, differs from many radiographic procedures where interpretation is mainly based on the expert evaluation of a trained radiologist. Therefore, strict attention to the performance of these devices is required. Inaccuracy or imprecision in individual measurements can lead to incorrect diagnosis. This becomes even more important in the evaluation of longitudinal measurements. For these reasons, a thoughtfully designed and carefully implemented scanner quality assurance (QA)/quality control (QC) program is required in all clinical and research installations. Quality assurance in medical applications involves methods of performance evaluation of equipment and the operator, to improve reliability of the results. Quality control, on the other hand, is an aggregate of sampling and testing procedures based on statistical theory and analysis, and is designed to ensure adequate quality of the finished product. In medical applications these two terms are often used interchangeably *(185)*.

Requirements for good quality measurements are different with respect to whether one wants to obtain a good trueness or a good precision (accuracy = trueness + precision). The trueness of a method (i.e., agreement of measured and true data) determines its ability to discriminate between healthy and osteoporotic subjects, or to assess fracture risk. A poor precision will limit diagnostic sensitivity by adding noise to the measurement result. More importantly, precision affects the ability of a method to monitor normal and pathological changes and to measure the response to therapy *(186,187)*. For monitoring purposes, it is essential to have excellent precision to determine response of a variable to disease or therapy. For diagnostic purposes, precision errors should be well below one T-score to minimize misclassification errors *(188−191)*.

Discussion

There are many sources of error for bone measurement in vivo, including surrounding soft tissue and foot positioning. Inter-subject variability and precision are influenced by soft tissue thickness, temperature and composition, and the quality of the sound transmission from the coupling medium into the skin. Additional errors may be introduced by the properties of the coupling medium between transducers and the skin itself (waterbath or sound transmitting pads) *(192−197)*. In the first part of this section, single error sources are described and interpreted with regard to their impact on measurement quality. Measures for assurance of good quality will be suggested in the second part.

Sources of Error

Positioning. As with other methods, anatomically consistent regions of the bone must be measured with QUS in order to obtain sufficient accuracy, while precision is affected by the quality of sequential repositioning for each patient (e.g. heel not parallel to the transducer, or not correctly adjusted to the foot positioner) *(193,197−199)*. There are different procedures for positioning that are implemented based on anatomical landmarks and/or acoustical criteria. Some devices are able to generate an image of the skeletal site (heel only). The use of an imaging system may help to overcome positioning errors by placing a ROI on the image *(200)*. In general, no advantage of imaging with respect to precision and the power of risk prediction, has been proven (OPUS, in-house data). However, for the individual subject, a measurement failure due to incorrect positioning is of great importance. Creation of an image enables control and documentation of the correct positioning by the operator. This is of particular importance for an interpreter to evaluate the validity of the test.

Soft Tissue Properties. The temperature of the skin and the subcutaneous tissue is variable and can influence QUS results *(201)*. Soft tissue temperature of the limbs can be substantially lower than regular body temperature, particularly in winter time. In the axial transmission method for radius, phalanges, or tibia measures are implemented to correct for the impact of soft tissue. In the cortical transverse transmission method for phalanges, temperature has little or no affect on measurements due to a large difference between SOS in the compact bone and soft tissue. This is different with heel

Table 6
Studies on QUS and Treatment for Prevention and Therapy of Osteoporosis

Study	Study design	Device	Study design	Yr	Parameter	Treatment	Control	p
Naessen et al. (166)	CS	Achilles	PM women (67 ± 1.2 yr)	−	BUA	Δ 1.1%	vs controls	*
			28 HRT		SOS	Δ 6.1%	vs controls	*
			28 nothing		Stiffness	Δ 12%	vs controls	*
Gonnelli et al. (169)	L	Achilles	PMO women (50−64 yr)	2	BUA	0.88%	−3.3%	n.s.
			78 CT + Ca		SOS	0.2%	−0.55%	*
			32 Ca		Stiffness	2.12%	−6%	*
Krieg et al. (171)	L	Achilles	PM women (62−98 yr)	2	SOS	−0.5%	−0.5%	n.s.
			124 CaVitD		BUA	+1.6%	−2.3%	**
			124 nothing					
Sahota et al. (172)	L	Achilles +	PM women (52.1 ± yr)	4	BUA	−1.6%	−8.1%	*
			30 HRT		SOS	+1.0%	−0.5%	n.s.
			30 nothing		Stiffness	+4.0%	−6%	*
Hadji et al. (173)	CS	Achilles +	PM women (52.2 ± 8 yr)	−	BUA	115.2	113	***
			611 HRT		SOS	1545.4	1540.2	***
			1395 nothing		Stiffness	89.5	86.7	***
Gonnelli et al. (168)	L	Achilles +	PMO women (55−65 yr)	4	BUA	1.9%	−2.3%	***
			74 AL + Ca		SOS	1.2%	−0.3%	***
			76 Ca		Stiffness	9%	−4%	***
Gonnelli (167)	L	Achilles +	OP men (48−68 yrs)	3	BUA	3.8%	−1.1%	***
			39 AL +Ca		SOS	0.4%	−0.2%	***
			38 Ca		Stiffness	6.0%	−2.0%	***
Balikian et al. (174)	L	UBA 575+	PM women (50−56 yr)	2	BUA	−17.8%	−14%	n.s.
			31 HRT					
			32 nothing					
Frost et al. (175)	L	Sahara	PM women (45−59 yr)	2	BUA	7.4%	1.6%	**
			39 HRT-Bs		SOS	8.3%	−4.8%	*
			25 HRT-Bs-2y 131			2y:4.4%		*
			nothing			2y:0.5%		
Moschonis and Manios(176)	L	Sahara	PM women (55−65 yr)	1	SOS	0.3%	0.0%	n.s
			42 Dairy (Ca + VitD)		BUA	2.0%	0.9%	n.s.
			40 nothing		QUI	2.2%	0.2%	n.s.
De Aloysio et al. (177)	L	DBM sonic 1200	PM women (52 + 2.5 yr)	1	UBPS	−2.8	−14.3	n.s.
			49 HRT		ADSoS	+0.7	−0.7	n.s.
			32 nothing					

Mauloni et al. (178)	L	DBM Sonic 1200	PM women (51.1 ± 3.2 yr)	4	AD-SoS	18 m/s	−38 m/s	*
			45 HRT		pSOS	30 m/s	−13 m/s	*
			67 nothing		BTT	0.12 μs	−0.04 μs	*
Zitzmann et al. (179)	L	DBM sonic 1200	Hypogonadal men (37.8 ± 14.3 yr) 54 T substituted	1	ADSoS	+2.46%	vs baseline	***
Ingle (183)	L	DBM sonic BP	PMO women (63 yr)	1	AD-SoS	−0.87%	−2.10%	n.s.
			18 AL 10 mg		BTT	7.0%	1.04%	**
			8 Ca		pSoS	1.37%	0.46%	**
Ingle et al. (183)	L	DBM sonic	PMO women (68 yr)	1	BTT	0.12 μs	0.01 μs	n.s
			10 ERT		pSoS	51 m/s	4 m/s	**
			11 nothing					
Gonnelli et al. (170)	L	Achilles + DBM BP	PMO women (62−76 yr)	1	BUA	−1.9%	0.2%	n.s
			30 TPD + Ca		SOS	0.2%	0.1%	n.s
			30 anti-resoprtive		Stiffness	−0.1%	−1.1%	n.s.
					AD-SoS	0.6%	1.1%	n.s
					BTT	−14%	1.5%	***
					FWA	17%	2.5%	***
Seriolo et al. (180)	L	DBM sonic 1200	PMO women with RA (45−55 yr) 20 antiTNFα + MTX + P 14 controls: MTX + P	1	AD-SoS	2.19%	−4.48%	**
Drake et al. (181)	L	Omnisense	PMO women (70.2 yr)	1	SOS Phalanx	Δ−5.5%	vs baseline	n.s.
			81AL 80 or 160 mg		SOS Radius	Δ−23.4%	vs baseline	*
Knapp et al. (182)	CS	Omnisense	PM women (58 yr)	−	SOS Phalanx	Δ 0.15 Z-sc	vs controls	n.s
			194 nothing		SOS Radius	Δ 0.44 Z-sc	vs controls	**
			126 HRT					

Abbr: PM, Postmenopausal; PMO, Postmenopausal Osteoporosis; AL, Alendronate; Ca, Calcium; Vit D, Vitamin D; TPD, Teriparatide; MTX, Methotrexate; P, Prednisone; HRT, Hormone Replacement Therapy; SCT, Salmon Calcitonin; RA, Rheumatoid Arthritis.

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

measurements, because SOS in trabecular bone and in soft tissue is similar. The impact of soft tissue temperature can be estimated using results from some studies in which skin temperature has been measured. A decrease of 3.6 m/s in SOS per one degree Celsius (C) increase in skin temperature has been observed *(197)*. In accordance with this result, a mean difference of 4 °C in skin temperature between winter and summer resulted in a mean difference of 15 m/s in SOS *(202)*, which corresponds to 0.5 T-score. The difference in stiffness was lower (0.25 T-score), and the difference in BUA was not significant. However, variations in individual skin temperatures can be even larger, by as much as 12°C *(197)*.

Precision can also be affected by variations in soft tissue thickness, which might be caused by gaining or losing weight, changes in diet (i.e. acute salt intake), or developing ankle edema *(203,204)*. For a dry system, a 6 mm decrease of heel thickness (caused by pressure to disperse edema) caused an increase of 24 m/s in SOS *(205)*. This effect can be explained by an increase of the bone to soft tissue ratio along the ultrasound path through the heel. For water-based systems, a much smaller effect can be anticipated because the acoustical parameters of edema and water are quite similar *(197,203,205)*.

Impact of the Coupling Medium. Unlike X-ray based technologies, achievement of good quality coupling of the ultrasonic beam into the body is essential. A coupling gel or liquid must be used in all methods to assure proper penetration through the skin. Devices with constant transducer separation use an additional coupling medium, usually water. Air bubbles in the water and variations in water temperature are possible error sources, which can be avoided by adding surfactants and using temperature control. In dry systems, errors may be caused by the temperature-dependence and aging of coupling pads *(185,197)*.

Recommendations for the Assessment of Good Measurement Quality

Use of QC Phantoms. One of the most important components of the QA program is the test object, which may be either a standard or a phantom *(185)*. A standard is an object of known acoustic properties, which does not attempt to resemble the anatomy of interest. It is usually a simple geometric form and can be used to test one or more specific aspects of the scanner performance. On the other hand, a phantom attempts to emulate the in vivo measurement as much as possible in terms of geometry and acoustic properties. Although the later is the more relevant, its manufacture is complex and expensive because the mode of ultrasound interaction with the medium is still unclear. Presently, there are no universally accepted QUS phantoms, but only "manufacturer-specific" phantoms, which are not anthropomorphic. Daily measurements of these phantoms are the primary method of detecting changes in the equipment that may result from component aging or outright failure (including electronics, mechanics, and the coupling path). As a result, in the case of longitudinal studies, one should be able to correct for an unstable device based on the drift or shift of the phantom

measurements, by applying a correction factor to the patient data *(195)*. This procedure would guarantee that the device's results reflect the "biological or therapeutic" reality and not a device malfunction. It is generally accepted that long-term stability and precision errors of measurements on these phantoms should not exceed a quarter of a T-score, in order to limit misclassification errors to a clinically acceptable level *(9)*.

Daily changes in QC parameters (e.g. SOS or BUA) may not reflect what happens in vivo because the reliability of these manufacturer-specific phantoms is influenced by external factors (e.g. air and water temperature, quality of the water, etc). Indeed, since they are usually stored at room temperature, the phantom, the room, or the water-bath could possess different temperatures from 1 d to another. In addition, the elasticity of the phantom material may change over time. As a consequence, it becomes very difficult to differentiate the effect of temperature from the actual instability of the system or the aging of the phantom. Therefore, more advanced QC procedures have been developed using, for example, a combination of external phantom and internal indicators based on the water measurements *(195)*. This approach enables a gain of confidence in the clinical outcome as well as in the manner one would have to correct the data in case of malfunction. As another alternative to the external phantoms, P. Laugier et al. suggested using internal digital phantoms, while Langton et al. suggested an external electronic phantom, designed to test scanner performance for BUA measurement *(206,207)*. Such phantoms are very stable, since they do not require any extra manipulation during the measurement and are not influenced by external factors. The digital BUA phantom concept has already been incorporated into one QUS device (UBIS 5000, DMS, France) and preliminary studies suggest encouraging results *(208)*.

Since differences between the devices of the same manufacturer have been observed *(13,209)*, specific cross-calibration procedures should also be implemented including exchange of QC phantoms. Cross-calibration between devices using different QUS-approaches is not feasible, because different skeletal sites may be measured with different technologies. Even with devices measuring the heel, methodologies differ (water-based/dry, calculation of variables) and it still must be evaluated if a cross-calibration is possible with sufficient accuracy. For this purpose several non-ultrasound device manufacturers developed external anthropometric "ultrasound specific" phantoms that are still under evaluation (Leeds QUS phantoms, CIRS QUS phantoms and the Vancouver Phantoms), with promising results *(185)*. Ideally, daily QC and initial cross-calibration between devices should be performed using a temperature-controlled anthropometric phantom mimicking trabecular structure.

QA/QC in Clinical Practice. Monitoring the performance and stability of the devices by regular quality control measurements using appropriate phantoms is a precondition for the assessment of good measurement quality. Also, QUS-specific training should be performed to raise the operator's awareness to the specific requirements of QUS measurements.

Indeed for most devices the operator has no influence over the study exam result after the signal has been recorded (i.e., no scan analysis).

Manufacturers may provide training of operators at the time of device delivery. This is typically a brief introduction to the software and patient handling. In addition to this, more extensive training is recommended. Training should include positioning and assurance of proper contact between the skin and the coupling medium. While proper positioning can be controlled using an image, a bad measurement quality through improper coupling can hardly be detected by the device and careful handling by the operator is necessary. An easy-to-implement method to evaluate for outliers is the performance of double measurements. This is not difficult, since QUS measurements are rapid and do not involve X-ray exposure. If differences between results of the two measurements remain within specific limits, reliability of the measurement is high. The limit could be three times the precision error of the variable: 95% of valid measurements should fall into this category. When this limit is exceeded, a third measurement should be performed to exclude outliers *(17,92)*.

Specific procedures can be recommended for known error sources, such as temperature and soft tissue thickness. Patients with severe edema should be excluded from heel measurements. In patients with low foot temperature SOS results will be falsely lower. This is not a problem when results are high. If numbers are in a range where consequences could result from the measurement, the foot should be warmed and measurement repeated.

An indirect way to evaluate technologist performance is by periodic assessment of reproducibility. This can be achieved by determining the coefficient of variation (CV) of the measurements. From time to time, a group of patients can be asked to undergo multiple measurements. By measuring a group of 15−30 subjects three or two times in a single visit, the measurement variability can be determined and precision evaluated. Whenever precision falls outside acceptable limits (still need to be defined for a given device and parameters) the technologist should have refresher training and proper technique should be reviewed. It is also necessary to determine if sufficient time is being allocated for each measurement. Often poor precision results from having too little time to prepare the patient or repeat measurements when an error is detected. The in vivo CVs generally quoted in the literature range from 0.8−5% and 0.2−1% for BUA and SOS, respectively (*see* Table 1). It is always recommended that precision assessment be performed by the QUS center's technologist and not rely on the precision values reported in the literature or by the manufacturer. Once the precision of the measurement is known, it is possible to determine the minimal detectable difference between two measurements that is statistically significant ($\sim$ least significant change). This information is useful in interpreting longitudinal measurements and assessing change. Since QUS is not recommended for monitoring a patient, the necessity of precision assessment in clinical practice is uncertain.

Additional Questions for Future Research

- What is an appropriate anthromorphic phantom for QC procedures that is acceptable for QUS devices on the market?
- What would be the impact in clinical practice of clearly defining QC procedures for all QUS devices?
- Should there be a standardized approach for the correction of measurement results using the patient's foot temperature?
- What are the acceptable limits for in vivo precision for a given device and parameters?

Summary

Heel QUS is inexpensive, transportable, ionizing radiation-free, and, like central DXA, proven to predict hip fractures and all osteoporotic fractures in elderly women. Unfortunately, the proliferation of bone ultrasound devices using different technologies for measuring different skeletal sites, together with the absence of technology-specific guidelines, has created great uncertainty in applying the results to the clinical management of individual patients. For the first time, The ISCD Official Positions, outlined in this document, describe the practical role of QUS in the management of osteoporosis based on the current state of scientific knowledge. The use and utility of QUS to identify subjects at low or high risk of osteoporotic fracture is justified particularly in situations where central DXA is unavailable. Heel QUS measures are related to global fracture risk with similar relative risk as other central bone density ROI for postmenopausal women and for men. Their use, in conjunction with CRF, allows for the identification of subjects who have either a sufficiently high probability of osteoporotic fracture and should initiate treatment, or a sufficiently low probability of osteoporotic fracture and therefore require no further medical investigation. Currently, however, QUS have not been shown to be effective in monitoring treatment efficacy. Further attention on quality control procedures as well as standardization, especially of ROI, could improve the utility and acceptance of these devices.

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