Quantitative ultrasound and bone health

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Abstract

This review of quantiative ultrasound (QUS) and bone health uses the current literature to summarise the clinical and research effectiveness of QUS. QUS has been demonstrated to have the ability to predict fracture, particularly at the hip. However, the magnitude of prediction is fracture-site, measurement-site and device dependent. The correlations between dual X-ray absorptiometry (DXA) and bone mineral density (BMD) are weak to moderate, resulting in different subjects being identified as being at risk of fracture by the two different methods. QUS is sensitive to age and menopause-related changes and to clinical risk factors and lifestyle factors associated with osteoporosis. Whilst a limited ability of QUS to monitor therapeutic intervention has been demonstrated, this is still an area where it's poorer precision, in comparison to DXA, results in limited applicability. Whilst DXA remains the gold standard for the diagnosis of osteoporosis, QUS may be of use for the prediction of those at risk of future fracture in areas where there is limited availability of DXA.

Key words: osteoporosis; ultrasound; bone density; fracture

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Resumen

En esta revisión sobre el Ultrasonido Cuantitativo (QUS) y su aplicación en la evaluación de la salud de los huesos, se analiza detalladamente la literatura disponible para conocer su papel y efectividad en la clínica cotidiana y en los programas de investigación. El QUS ha probado ser útil para predecir fracturas, especialmente de la cadera. Sin embargo, la exactitud de la predicción depende del sitio de fractura que se desea evaluar, del sitio anatómico donde se realiza la medición y de los diferentes instrumentos. La correlación que existe entre densitometría de rayos X (DXA) y QUS puede ser débil a moderada, porque ambos métodos determinan diferentes componentes de la masa ósea relacionados con la presentación de las fracturas. El resultado del QUS como el del DXA también es sensible a la edad, cambios relacionados con la menopausia, a factores de riesgo clínicos y de estilo de vida relacionados con la osteoporosis. Se ha demostrado que el QUS puede servir para monitoreo de las intervenciones terapéuticas, de manera menos sensible que el DXA, lo que limita su aplicación con este propósito. El DXA sigue siendo el estándar diagnóstico de oro para la osteoporosis; la capacidad del QUS para predecir fracturas, lo vuelve una buena alternativa en lugares y/o países donde el acceso a DXA tiene limitaciones.

Palabras clave: osteoporosis; ultrasonido; densidad ósea; fractura

The use of quantitative ultrasound (QUS) for the measurement of bone was first reported by Langton *et al.* in 1984. Since 1984, the use of QUS has expanded vastly, and it has been widely used for research and clinical purposes.[1] The first ultrasound system reported by Langton used transmission mode ultrasound with a transmitting and a receiving transducer placed either side of the calcaneus, which was placed within a water bath.[1] The calcaneus was chosen as a site for measurement since it is easily accessible, with the

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medial and lateral aspects being relatively flat and parallel. It contains approximately 90% trabecular bone, which has a high metabolic turnover rate and a pattern of bone loss similar to the spine.[2,3] The majority of subsequent ultrasound systems have been based upon this prototype, although dry systems which use ultrasound gel as a coupling medium instead of water have also been introduced. Much of the research done into QUS has therefore been performed using ultrasound measurements of the calcaneus. However, there have also been devices introduced that measure the patella, tibia, phalanges, radius and metatarsal, using a range of techniques including transmission and semi-reflection or axial transmission mode ultrasound.[4-10]

Dual X-ray absorptiometry (DXA) is currently the most widely used tool in the United Kingdom for the measurement of bone mineral density (BMD) and is widely regarded as the gold standard for the diagnosis of osteoporosis and fracture prediction. However, in many areas there are inadequate resources to meet the demand.[11] Quantitative ultrasound offers a radiation-free, inexpensive, non-invasive alternative to DXA.[11,12]

What QUS measures

A number of authors have investigated the ability of QUS to measure the density and micro-architectural properties of bone.[3,13-18] Results from in-vitro studies in bovine bone have found the ultrasound derived modulus of elasticity correlates strongly with values of bone breaking strength derived from static loading.[19-21] A number of studies have reported QUS parameters to be significantly associated with bone structure independently of BMD.[3,16-18,20] Whilst Mehta *et al.* reported ultrasound velocity and elasticity to be strongly connected with material elasticity as measured by mechanical testing.[14] Broadband ultrasound attenuation (BUA) values have been reported to be dependent upon trabecular orientation *in vitro*.[22,23] However, high correlation's *in-vivo* of r=0.75 to r=0.90 between BUA and BMD at the calcaneus using QUS and DXA with matched regions of interest have been reported,[24,25] suggesting that QUS may reflect micro-architecture, but only to a small extent. Njeh *et al.* in a comprehensive review of whether QUS is dependent on structure concluded that ultrasound attenuation is due to structural parameters as well as dependent on density.[15]

Precision

QUS has demonstrated limited use in the monitoring of patients undergoing treatment, primarily due to its poor precision in comparison with DXA, leading to long time intervals being required to detect changes in bone.[26-28] The precision of QUS is generally reported to be poorer than that of DXA. There are currently QUS devices available for measuring a range of anatomical sites including both predominantly trabecular and predominantly cortical bone sites. The calcaneus is a site with a high trabecular bone content, whilst some other sites of measurement are primarily cortical. When measuring the speed of sound (SOS), the coefficient of variation can appear particularly favourable for cortical sites due to the higher SOS in cortical bone compared to trabecular bone. When the coefficient of variation is calculated for cortical bone, division by a larger denominator is applied than for measurements in trabecular bone, giving the appearance of better precision at the cortical sites. Broadband ultrasound attenuation precision also appears to be poorer than its corresponding SOS precision in the same devices for the identical reason. As such, it is difficult to compare precision results between ultrasound devices and different anatomical regions. In order to make a useful comparison the precision results need to be standardised (standardised precision – SP) to the population standard deviation, signifying the error within the useful clinical range, of the individual device. Frost *et al.* found short term precision to range from 0.3-0.4% (SP 0.16-0.23) in the Hologic Sahara[29] and 1.21-1.62% (SP 0.14-0.19) for the Osteometer DTU-1.[30] Precision results for the Sunlight Omnisense have been reported to range from 0.2 to 1.48% depending on the anatomical site measured.[31-33]

As a result of the poor precision of QUS in comparison to DXA, optimisation of measurements to reduce precision errors is of utmost importance. Parametric imaging has been introduced on some calcaneal scanners in an attempt to improve precision.[30,34] In contrast to the fixed transducers of many calcaneal systems, the Sunlight Omnisense uses hand-held probes to enable measurement of multiple peripheral sites (figure 1).[33] This has the potential to influence the precision results, especially inter-operator precision. Operator training is therefore particularly important on this device to minimise precision errors.

Age-related changes

QUS has been demonstrated to be sensitive to age-related, pubertal stage and menopause-related changes in bone.[5,27,32,33,35-37] Multi-site quantitative ultrasound has demonstrated differing peak bone mass for different sites, with the weight bearing sites tending to peak earlier and have a lower rate of bone loss postmenopausally.[32,33] Studies evaluating premenopausal age related changes

Figure 1. Measurement of the third proximal phalanx using the Sunlight Omnisense

at the phalanges using the DBM-sonic have also found age-related bone loss premenopausally.[4,5]

Correlation with DXA

The correlation of QUS measurements with BMD has generally yielded weak to moderate correlations, particularly when peripheral QUS measurement sites have been correlated with axial BMD.[7,33] Faulkner *et al.* found correlations ranging from 0.26-0.63 for calcaneal QUS and DXA of the spine, hip, forearm and whole body.[38] He et al found correlations ranging from 0.30-0.41 for calcaneal QUS parameters and whole body DXA and correlations ranging from 0.28-0.41 between calcaneal QUS and proximal femur BMD regions of interest (ROI's).[39] Site matched correlations between BUA, velocity of sound (VOS) and BMD at the calcaneus have given better correlations ranging from 0.66-0.73.[20] Some of the highest site matched correlations have been reported by Chappard *et al.* and Laugier *et al.* Chappard *et al.* reported high correlations in vivo of 0.78-0.90 between BUA and BMD at the calcaneus from their study using imaging QUS and DXA where site matched regions of interest were able to be correlated.[24] In a similar study Laugier *et al* used imaging QUS and QCT in cadavers to investigate the relationship between site matched measurements of BUA and BMD and reported high correlations of r=0.75-0.88.[25]

Fracture discrimination

Quantitative ultrasound measurements at the calcaneus have been demonstrated to be able to discriminate between cases and controls with vertebral crush fractures and non-spine fractures.[1,10,27,39-45]

Some of the earliest strongest evidence to support the use of QUS for discriminating between osteoporotic fractures and controls has come from large prospective studies. The first of these was published in 1990, when Porter *et al.* measured 1 414 women over the age of 69 who were in residential accommodation.[46] Measurements were performed at the calcaneus using the original Langton device. The women were followed up over a period of two years during which time a total of 73 women suffered a hip fracture. The fracture group was found to have a lower BUA than the non-fracture group and were also found to be more active and have a lower cognisance score. Table I outlines a number of cross-sectional and prospective studies demonstrating the ability of QUS measurements at various sites to predict osteoporotic fracture. In all these studies, QUS is a good predictor or discriminator of hip or non-spine fractures.[9,45,47-53] In a meta-analysis of QUS and fractures, Marín *et al.* reported the strength of association between QUS with non-spinal fractures to be similar to axial or peripheral BMD measurements. However, QUS was shown to be inferior to the association between BMD measured at the hip and hip fracture.[54] Despite its ability to predict non-spine and hip fractures, the data to support the ability of QUS to predict vertebral fractures is variable. However, calcaneal QUS generally has better prediction and discrimination of vertebral fracture than other sites.[27,33,55-64]

Risk factors and secondary osteoporosis

Studies have found QUS to be sensitive to clinical risk factors for osteoporosis and secondary causes of osteoporosis. Frost *et al.* reported calcaneal QUS to be as sensitive as BMD measurements to clinical risk factors for osteoporosis.[65] Stewart *et al.* also reported QUS measurements to be sensitive to clinical risk factors for osteoporosis, but reported the strength of the association to be dependent upon the type of QUS device and the variable measured.[66]

Other studies have reported QUS parameters to be decreased in subjects with renal disease,[67,68] Crohn's disease,[69] primary hyperparathyroism,[70-73] Rheumatoid arthritis[74] and glucocorticoid use.[6,75] Children and young adults with severe cerebral palsy and taking anticonvulsant therapy (with and without fractures) have been demonstrated to have reduced QUS measurements at the calcaneus.[76] Damilakis *et al.* reported a negative correlation of SOS measurements at the radius and tibia with duration of type 1 diabetes in adolescents.[77] However, other authors have reported limited usefulness of QUS in patients with rheumatoid arthritis and with inflammatory bowel disease.[78-80]

Table I
EXAMPLES OF STUDIES INVESTIGATING OSTEOPOROTIC FRACTURES AND QUANTITATIVE ULTRASOUND*

Study	*Design*	*# site*	*QUS measurement*	*QUS measurement site*	*Age- adjusted relative risk / odds ratio*
Heaney 1995	1	Vertebral	VOS	Patella	2.11 (1.14-3.91)
Bauer 1995	2	Vertebral	BUA	Calcaneus	1.8 (1.4-2.3)
Gluer 1996	2	Hip	BUA	Calcaneus	1.9 (1.5-2.4)
Hans 1996	1	Hip	BUA	Calcaneus	2.0 (1.6-2.4)
Bauer 1997	1	Hip	BUA	Calcaneus	2.0 (1.5-2.7)
Mele 1997	1	Non-spine	Ad-SOS	Phalanx	1.5 (1.1-1.7)
Pluijm 1999	1	Hip	BUA	Calcaneus	2.3 (1.4-2.7)
Gnudi 2000	1	Non-spine	SOS	Radius	3.69 (1.18-11.49)
				Patella	3.89 (1.53-9.90)
Huopio 2004	1	All	SOS	Calcaneus	1.80 (1.27-2.56)
Bauer 2007	1	Hip Non-spine	BUA	Calcaneus	2.0 (1.5-2.8) 1.6 (1.4-1.8)

* The QUS measurement parameter displayed is that which provided the optimum predictive power in the study outlined

1= prospective, 2= cross-sectional

Lifestyle factors

Physical activity has been demonstrated to have a positive effect on calcaneal QUS parameters.[81-86] QUS measurements have also been demonstrated to be reduced in smokers compared to non-smokers.[87,88]

T-score equivalence with DXA

The World Health Organisation (WHO) criteria[89] cannot be used with QUS to diagnose osteoporosis,[90] although QUS can be useful as an indication of osteoporosis. A number of authors have reported site and device specific T-score equivalence to DXA.[91-99] These studies demonstrate that a single diagnostic threshold for QUS is not appropriate and T-score equivalence to DXA is site- and device-specific.

Monitoring therapy

The poorer precision of QUS in comparison to DXA has resulted in limited applicability for longitudinal use to monitor disease progression or therapeutic intervention. The international QUS consensus group report in 1997 recommends further study of the use of QUS to monitor disease progression or response to therapy,[100] whilst the National Osteoporosis Society in the UK at present does not recommend the use of QUS for monitoring treatment and states that DXA should be used instead.[101]

Cross-sectional studies of QUS have demonstrated its ability to differentiate between patients treated with HRT compared to age-matched controls.[102-104] These data are at variance with some of the research into the effect of HRT on calcaneal QUS parameters, which have found limited effects.[10,105,106] However, Sahotal *et al.* found a positive effect of HRT at the calcaneus in a longitudinal study over a four year period, although the individual increases for BUA and SOS were not as great as found for lumbar spine and total hip BMD.[26]

A number of longitudinal studies have demonstrated a response of QUS to patients treated with bisphosphonates at the calcaneus and tibia.[107-110] However, as a result of the poorer precision, the follow-up period is generally required to be longer than that of DXA.[109]

In conclusion, QUS has been extensively researched and has been demonstrated to have the ability to predict fracture, particularly at the hip. However, the predictive ability of QUS appears to be fracture-site, measurement-site and device specific. The correlations between DXA and BMD are weak to moderate, resulting in different subjects being identified as being at risk of fracture by the two different methods. QUS is sensitive to age and menopause-related changes and to clinical risk factors lifestyle factors associated with osteoporosis. Whilst a

limited ability of QUS to monitor therapeutic intervention has been demonstrated, this is still an area where its poorer precision, in comparison to DXA, results in limited applicability. Whilst DXA remains the gold standard for the diagnosis of osteoporosis, QUS may be of use for the prediction of those at risk of future fracture in areas where there is limited availability of DXA.

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