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Quantitative ultrasound for the detection and management of osteoporosis

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Abstract

Quantitative ultrasound (QUS) appears to be developing into an acceptable, low-cost and readily-accessible alternative to dual X-ray absorptiometry (DXA) measurements of bone mineral density (BMD) in the detection and management of osteoporosis. Perhaps the major difficulty with their widespread use is that many different QUS devices exist that differ substantially from each other, in terms of the parameters they measure and the strength of empirical evidence supporting their use. But another problem is that virtually no data exist outside of Caucasian or Asian populations. In general, heel QUS appears to be most tested and most effective. Some, but not all heel QUS devices are effective assessing fracture risk in some, but not all populations, the evidence being strongest for Caucasian females > 55 years old, though some evidence exists for Asian females > 55 and for Caucasian and Asian males > 70. Certain devices may allow to estimate the likelihood of osteoporosis, but very limited evidence exists supporting QUS use during the initiation or monitoring of osteoporosis treatment. Likely, QUS is most effective when combined with an assessment of clinical risk factors (CRF); with DXA reserved for individuals who are not identified as either high or low risk using QUS and CRF. However, monitoring and maintenance of test and instrument accuracy,

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Resumen

El ultrasonido cuantitativo (QUS) es una alternativa para la detección y manejo de la osteoporosis de bajo costo y uso práctico, si se compara con las densitometrías de rayos X de doble haz de baja energía (DXA) que determinan densidad mineral ósea (BMD). La mayor dificultad para el uso generalizado del QUS por un lado es que existen muchos instrumentos que son significativamente diferentes uno del otro y por otro en la calidad de la evidencia en que se justifica su empleo, que generalmente es insuficiente y/o poco sistematizada. Otro problema importante del QUS, es que prácticamente no existe información que no sea la generada en poblaciones asiáticas o caucásicas. En general, los estudios de calcáneo realizados con QUS son los más utilizados y mejor validados para evaluar el riesgo de fracturas en algunas poblaciones. La evidencia más grande de su efectividad se conoce para las mujeres caucásicas y asiáticas mayores de 55 años e incluso para los hombres asiáticos mayores de 70 años. Varios instrumentos cuentan con buen sustento científico, que los vuelve confiables para establecer un pronóstico preciso e identificar el riesgo individual de sufrir fracturas por osteoporosis, sin embargo, existe poca evidencia que respalde su uso para iniciar y monitorear el resultado del tratamiento de la osteoporosis. El QUS mejora su efectividad diagnóstica cuando se combina

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precision and reproducibility are essential if QUS devices are to be used in clinical practice; and further scientific research in non-Caucasian, non-Asian populations clearly is compulsory to validate this tool for more widespread use.

Key words: Quantitative ultrasound; osteoporosis; fragility fracture; dual-energy X-ray absorptiometry; evidence-based practice

con los resultados de un cuestionario que identifica riesgos clínicos. En un escenario ideal, el DXA se debe reservar solo para aquellos individuos que no puedan ser identificados de manera confiable usando QUS y el cuestionario de riesgos clínicos. Si se quiere aceptar a los instrumentos QUS en la práctica clínica, para el monitoreo es indispensable asegurar y mantener la exactitud, precisión y reproducibilidad de los instrumentos y de los técnicos que los utilizan. Se requieren más estudios científicos de poblaciones no caucásicas o asiáticas para validar el uso generalizado del QUS.

Palabras clave: ultrasonido cuantitativo; osteoporosis; fractura por fragilidad; densitometría de rayos X; práctica basada en evidencias

Osteoporosis is a “disease characterized by low bone mass and micro-architectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk”.¹ Hip fractures are especially problematic. In the US, for example, more than 250 000 hip fractures occur annually,²⁻⁵ at least 90% of which are attributed to osteoporosis; women over 70 years of age are particularly vulnerable.^{6,7} Those who sustain a hip fracture often suffer severe and prolonged physical and social limitations:^{6,8-13} only 15% of patients are able to walk without assistance 6 months after the event; 50% never return to their previous functional state; and roughly 20% require long-term care.^{14,15} Hip fracture patients also experience a 20% increase in mortality over the next five years. Even in relatively smaller-population countries like Canada, costs to governments measure in the billions of dollars annually, related both to direct health care costs and insurance.¹⁴ And, as much of a problem hip fractures currently are, the numbers almost certainly will increase dramatically as an increasing percentage of the population achieves older age, with as many as 6.3 million hip fractures predicted worldwide, annually, by 2050.¹⁶

Osteoporosis is a major public health concern in Latin America as well, with vertebral osteoporosis affecting 12-18% and femoral osteoporosis 8-22% of women 50 years and older.^{17,18} Bone mineral density may be lower in Latin American women over 50 than in their American counter-parts,¹⁹ with osteopenia affecting almost 60% of women ≥ 50 .¹⁸ In addition, in Latin America, up to 362 osteoporosis-related hip fractures occur annually per 100 000 persons 50 years and older;¹⁷ vertebral fractures affect almost one in five women over 50;^{17,18} and between 17 and 37% of hip fracture sufferers die within a year of their fracture.¹⁷ The social burden of osteoporosis also is high in South and Central America.

Across 20 Latin American countries, including Mexico, direct costs have ranged from \$4 500 to \$6 000, which is higher than the per capita gross incomes of many Latin American countries, which range from \$410 to \$7 550.¹⁷

For a variety of reasons that include the huge impact osteoporosis-related fractures have upon individuals and society, increased health expectations among seniors, and recent advances in the prevention and treatment of osteoporosis, the early detection of osteoporosis now is considered essential. Traditionally, measurement of bone mineral density (BMD) via dual-energy x-ray absorptiometry (DXA) has been the means by which osteoporosis is diagnosed and fracture risk estimated.²⁰ In 1994, the World Health Organization (WHO) published a set of diagnostic criteria to define osteoporosis in postmenopausal Caucasian women,²¹ using BMD values measured by DXA. These criteria express BMD relative to the mean BMD of a healthy young-adult reference population, expressed as a T-score, which represents the number of standard deviations a measured BMD is from the reference population mean. These WHO criteria commonly are applied to BMD measurements at the spine, hip, and forearm,²² and define osteoporosis as a T-score of -2.5 or less; in other words, a given individual is said to have osteoporosis if her or his BMD is more than 2.5 standard deviations less than the mean BMD of a healthy, young adult.

Because of the high socio-economic impact of hip fractures and studies which demonstrate that BMD measurements at the proximal femur are most strongly associated with hip fracture, current clinical treatment guidelines for osteoporosis generally are based upon DXA measurements of BMD at the hip—at the femoral neck, for the hip measured in total, or using both measurements.²³ This being said, a variety of problems exist

with DXA, which include difficulties extrapolating standards for hip fracture risk to other skeletal sites, like the wrist and lumbar spine. Two other major problems with DXA that are especially pertinent in South and Central America are (1) its cost, and (2) the rarity of DXA instruments in many localities, especially in poorer and/or rural areas and in less developed countries. These two latter problems have led many investigators to search for some lower-cost and more readily-available alternative to DXA for the diagnosis of osteoporosis and/or the estimation of future risk of fragility fractures; and one such alternative that has garnered considerable recent attention has been quantitative ultrasound (QUS).

Quantitative ultrasound: General principles

Initially used to detect enemy submarines underwater during World War II, ultrasonic waves are sound waves outside the threshold of human hearing, which pass easily through fluid and other tissues, and which are altered upon contact with bone, in terms of their shape, intensity and speed. Over the years, ultrasonic (US) devices have found a diverse array of clinical applications in medicine, including uses in cardiology to assess cardiac size and function and vascular flow, obstetrics to assess fetal development, general medicine to examine for intra-abdominal and intra-peritoneal masses, and rheumatology and orthopedics to both diagnose and treat conditions like bursitis and tendonitis. As opposed to qualitative ultrasound, which just generates pictures, quantitative ultrasound uses ultrasonic waves at lower frequencies to generate empirical measurements.

With respect to the detection of osteoporosis, QUS can be used to measure a variety of parameters that pertain to bone density, parameters that are related to the velocity and attenuation of US waves as they pass through bone. Advantages of QUS over DXA are that it is inexpensive, transportable, and ionizing radiation free. The low cost and transportability could make QUS an especially valuable osteoporosis detection tool wherever cost or instrument inaccessibility renders DXA difficult or impossible. But does QUS work? Already, there is evidence that QUS is as effective as axial DXA in predicting hip fractures and all osteoporosis-related fractures in elderly women.²⁴⁻²⁶ Having said this, numerous potential problems still exist with the use of QUS for osteoporosis detection. For example, care must be exercised interpreting US velocity and attenuation, as they are calculated differently depending upon the manufacturer and model of the ultrasound device. Similarly, there are significant differences between QUS instruments from different manufacturers, differences

that affect the interpretation of results and limit comparisons between devices.

Different QUS devices

QUS devices can be classified into three types, related to the form of US transmission used:

1. Trabecular sound transmission is the most commonly utilized category of devices, for which the most evidence exists supporting its use. It is best utilized measuring the heel.^{24,25}
2. Cortical transverse transmission currently only is used in phalanx contact devices;²⁷ to date, little evidence supports the use of these devices clinically for osteoporosis.
3. Cortical axial transmission presently is being investigated for use in phalanges, the radius and the tibia;²⁷ no clinical application have been proven, to date.

As just noted, heel devices currently appear to have the most clinical applications, with some devices –like the GE-Lunar Achilles and the Hologic Sahara– better tested and more proven effective than others (table I). For these purposes, the recommended parameter of interest generally has been the heel stiffness index (SI) or the Quantitative index (QUI), which is a composite score combining the results of broadband ultrasound attenuation (BUA) and speed of sound (SOS), as measured in meters per second.

The remainder of this paper will review the clinical use of QUS in the following settings: 1) the prediction of fracture risk; 2) the diagnosis of osteoporosis; 3) the initiation of osteoporosis treatment or prevention; 4) the monitoring of such treatment; and 5) osteoporosis case finding. The paper will conclude by examining 6) quality assurance and quality control issues pertaining to the clinical application of QUS.

1) Using QUS to predict fracture risk

At the present time, there is satisfactory (cross-sectional and/or prospective) evidence that QUS can be used to assess fracture risk in some, but not all populations, as defined by sex, age and ethnic background.²⁸⁻⁹⁶ This is particularly true of heel QUS and for hip versus spinal fractures. Having said this, because of various methodological issues, it is difficult to compare studies. Nonetheless, combining the results from 13 studies involving 9 561 patients,^{33,39,40,43-45,48,52,58-60,69,79} it is reasonable to state that the increase in relative risk observed for each standard deviation decrease in stiffness index (SI),

Table I
QUANTITATIVE ULTRASOUND (QUS) DEVICES CURRENTLY AVAILABLE

<i>Manufacturer</i>	<i>Model</i>	<i>Ability to assess hip fracture risk</i>	<i>Ability to assess spine fracture risk</i>	<i>Ability to assess all fracture risk</i>
GE-medical (Lunar)	Achilles	Proven in most populations	Proven in most populations	Proven in most populations
DMS	Ubis 3000/5000	Some evidence	Some evidence	Some evidence
Hologic	Sahara	Proven in Caucasians	Proven in Caucasian females	Proven in Caucasians
Norland (McCue)	Cuba Clinical	Proven in Caucasians	Some evidence	Proven in Caucasians
IGEA	DBM Sonic BP	Proven in Caucasian females	Proven in Caucasian females	Some evidence
BeamMed (Sunlight)	Omnisense	Some evidence	Some evidence	Some evidence
Meditech	DTU-One	No evidence	Some evidence	Some evidence
Aloka	AOS-100	Some evidence	No evidence	No evidence
Medilink	Osteospace			
Quidel Inc.	QUS-2			
Ishikawa Seisakusho Ltd.	Benus			
Elk Co.	CM-100 / 200	No Evidence		
Osteosys Co.	Sonost 2000 / 3000			
BMtech21 Co.	Osteolmager Plus			
BMtech21 Co.	Osteo Pro			

Data gleaned from Quantitative Ultrasound (QUS) in the Management of Osteoporosis: The 2007 ISCD Official Positions

measured at the heel using QUS, is roughly 2.0 for the hip and spine, and approximately 1.5 for all fractures combined. Consequently, heel QUS is much the same as DXA BMD, in terms of hip and spine fracture risk per standard deviation decrease.^{97,98}

Although some differences may exist in the expression of osteoporosis and overall fracture risk in Hispanics versus general Caucasians and other ethnic populations,^{99,100} there is ample empirical evidence that the heel QUS stiffness index, using some but not all QUS devices, is predictive of hip fracture risk in Caucasian and Asian women over age 55, and of any fracture risk in Caucasian women > 55 (table II). Weaker evidence exists that the heel QUS stiffness index, again using some but not all QUS devices, is predictive of hip fracture risk in Caucasian and Asian men over age 70; of vertebral fracture risk in Caucasian and Asian women over age 55; and of any fracture risk in Asian women and Caucasian or Asian men > 70. With respect to QUS devices from one of the other two categories, phalanx QUS devices utilizing cortical transverse transmission might predict non-vertebral fracture risk in Caucasian women > 70; however, to date, cortical axial transmission devices have no proven clinical application.

Another practical question is: which QUS device is best to use? As indicated in table I, the GE Lunar Achilles and the Hologic Sahara are among the best tested

devices, at the hip, spine and overall, and both seem effective for most females; the former may be preferable in males. Some evidence exists supporting the use of the Norland Cuba Clinical and the IGEA DBM Sonic BP, at least among Caucasians. However general results on the IGEA DBM Sonic device are not very impressive. Consequently, the three heel devices appear to be the most reasonable to use, at this time, though further testing of these and other devices clearly is necessary.

2) Using QUS to diagnose osteoporosis

Diagnosing osteoporosis using QUS is less supported by evidence and more complicated and problematic than assessing fracture risk is. To start with, the T-score diagnostic criteria of -2.5, classically used for DXA BMD, cannot be applied to QUS without discrepancies in the numbers of women diagnosed with osteoporosis. This is because there are tremendous variations in QUS measurements by skeletal site, and because different QUS devices yield different results. If, for example, the prevalence of osteoporosis is defined as -2.5 standard deviations from the mean threshold for QUS, even within the same sample population, different QUS instruments and different skeletal sites generate prevalence estimates that vary as much as ten-fold; for example, prevalence estimates among Caucasian women > 65 have ranged

Table II
USING QUANTITATIVE ULTRASOUND (QUS)
TO ASSESS FRACTURE RISK

Device	Population studied	Skeletal site studied	Strength of evidence
Some, but not all heel QUS devices	CF > 55 y/o	Hip	Good
Some, but not all heel QUS devices	AF > 55 y/o	Hip	Fair
Some, but not all heel QUS devices	CM > 70 y/o	Hip	Fair
Some, but not all heel QUS devices	AM > 70 y/o	Hip	Fair
Some, but not all heel QUS devices	CF > 55 y/o	Spine	Good
Some, but not all heel QUS devices	AF > 55 y/o	Spine	Poor
Some, but not all heel QUS devices	CF > 55 y/o	Overall	Good
Some, but not all heel QUS devices	AF > 55 y/o	Overall	Fair
Some, but not all heel QUS devices	CM > 70 y/o	Overall	Fair
Some, but not all heel QUS devices	AM > 70 y/o	Overall	Fair
Phalanx cortical transverse transmission devices	CF > 70 y/o	Non-vertebral	Fair

CF= Caucasian females; AF= Asian females; CM= Caucasian males; AM= Asian males

from 4 to 50%.^{96,101-105} To overcome this dilemma, there is a need for pre-defined, device-specific diagnostic thresholds. One recommended system suggests calibrating QUS measurements with DXA results, the latter used as the 'gold standard', so that an upper QUS threshold is set to identify osteoporosis with 90% sensitivity, and a lower threshold is set to identify osteoporosis with 90% specificity.^{106,107} A similar approach already has been recommended by the UK National Osteoporosis Society to define upper and lower thresholds for pDXA,^{108,109} the results of which are highly correlated with QUS. Using such a system, one could identify osteoporosis with high probability in patients whose results fall below the lower threshold for QUS, where specificity exceeds 90%; between the upper and lower thresholds, the diagnosis of osteoporosis would be considered quite equivocal, so that another means of measurement, like DXA BMD, would be highly recommended; and above the upper threshold for QUS, where the sensitivity of a value below the threshold is 90%, osteoporosis would be deemed unlikely.

We, in fact, utilized this approach in 5 954 women 75 years and older who took part in the EPIDOS Study, utilizing the 90% sensitivity threshold for the Achilles stiffness index of SI= 78%, and the 90% specificity threshold of SI= 57%. Using these cut-off points generated 11% false positive (FP) and 13% false negative (FN) results, which are comparable to the FP and FN rates of

many other tests. Based upon these results, we believe that device-specific heel QUS thresholds for 90% sensitivity and 90% specificity in specific populations defined by sex, age, and ethnic background, can be used to identify individuals who have either a high or a low likelihood of osteoporosis, even though only limited evidence exists supporting the use of any existing QUS device for this purpose. Devices that have been evaluated include the GE-Lunar Achilles, the Hologic Sahara, and the DMS UBIS-5000, each of which uses a different measure and different upper and lower likelihood thresholds, as indicated in table III. What can be concluded is that, regardless of the QUS device used, values that fall between the upper and lower thresholds strongly warrant further evaluation using DXA BMD as a more definitive test.

3) Using QUS to initiate osteoporosis treatment

Except in patients with a low-energy fracture of the hip or spine, when the fracture alone is adequate to require treatment, all currently-published guidelines or recommendations for the initiation of osteoporosis treatment are based upon DXA BMD values; in no instance, to date, are the results of QUS the definitive parameter. Despite this, several studies have demonstrated high levels of correlation ($r \sim 0.90$) between heel trabecular sound transmission and BMD at matched skeletal sites.¹¹⁰⁻¹¹³ Moreover, both SOS and BUA, standard QUS measurements, are dependent upon overall bone strength which, in turn, is related to bone density, architecture and turnover, and the extent of bone mineralization.^{110,112,114-121} These factors likely work together to maintain overall bone quality and strength, and to prevent fractures and other bone failure.^{110,112,114-121} QUS parameters related to heel trabecular transverse transmission are highly correlated with bone strength.^{117,122-129} Consequently, it is conceivable that guidelines could be created using QUS to guide when to initiate osteoporosis treatment,

Table III
USING QUANTITATIVE ULTRASOUND (QUS) TO DIAGNOSE
OSTEOPOROSIS

Device	Population studied	Threshold for high likelihood of osteoporosis	Threshold for low likelihood of osteoporosis
GE-Lunar Achilles	CF and AF > 65	SI \leq 57.0	SI > 78
Hologic Sahara	CF and AF > 65	QUI \leq 59.0	QUI > 83
DMS UBIS-5000	CF and AF > 65	BUA \leq 55.0	BUA > 62

CF= Caucasian females; AF= Asian females

especialmente si se combinan con el uso de factores de riesgo clínicos.¹³⁰ Hasta la fecha, sin embargo, no se han publicado ensayos clínicos aleatorizados que examinen si los individuos identificados como alto riesgo de fractura por QUS responden al tratamiento.

En el presente momento, la evidencia publicada no respalda el uso de QUS con valores específicos de dispositivo para iniciar el tratamiento de la osteoporosis en mujeres más jóvenes que 65 años o en hombres de cualquier edad, pero sí existe evidencia que respalda el uso de QUS en otras poblaciones, cuando la DXA no está disponible. Estas poblaciones incluyen 1) mujeres caucásicas y 2) mujeres asiáticas que están entre las edades de 65 y 74 años, exhiben resultados por debajo del umbral específico de dispositivo (i.e. $SI \leq 57.0$ con el dispositivo GE-Lunar Achilles), y tienen al menos dos factores de riesgo clínicos (tabla IV); y 3) mujeres caucásicas y 4) mujeres asiáticas que tienen 75 años o más, exhiben resultados por debajo del umbral específico de dispositivo (i.e. $SI \leq 57.0$ con el dispositivo GE-Lunar Achilles), y tienen al menos un factor de riesgo clínico además de la edad. La tabla IV lista los factores de riesgo clínicos pertinentes que hemos identificado al examinar los meta-análisis publicados, así como las revisiones de literatura escritas por Kanis¹³¹ y Durosier.⁹⁸

Actualmente, la Organización Mundial de la Salud (OMS) está desarrollando un modelo para predecir la probabilidad de fracturas relacionadas con la osteoporosis, combinando las mediciones de densidad mineral ósea (BMD) en el cuello femoral por DXA y los factores de riesgo clínicos (CRF). Esto también podría hacerse combinando QUS y CRF, usando una puntuación T específica de dispositivo. Los valores altos y bajos de probabilidad de riesgo generados por QUS—por ejemplo, $SI \leq 57.0$ y > 78 , respectivamente, para el dispositivo GE-Lunar Achilles—podrían usarse para decidir si el tratamiento está justificado. Debido a que los dispositivos tienen sus propios valores de umbral de probabilidad que todos corresponden a niveles de riesgo de fractura similares, este enfoque podría ser

utilizado independientemente del instrumento de medición utilizado. Los resultados preliminares que demuestran los beneficios de este enfoque combinado de CRF y tecnología QUS ya han sido publicados por Hans *et al.*¹⁴²

Desafortunadamente, mientras que QUS y BMD están altamente correlacionados en el hueso trabecular¹⁴³ y esta correlación es razonablemente bien entendida, la situación es considerablemente más compleja con las mediciones corticales. Muchas propiedades influyen en estas mediciones, incluyendo el espesor cortical, la mineralización, la porosidad y la estructura lamelar, y no está claro hasta qué grado estas varias propiedades contribuyen a la fuerza ósea.¹⁴⁴⁻¹⁴⁷ Como consecuencia, los dispositivos QUS que miden el hueso cortical, como los dispositivos de transmisión transversal cortical actualmente utilizados para evaluar las falanges, y los dispositivos de transmisión axial cortical que están siendo investigados para su uso con falanges, la muñeca y la tibia, no se recomiendan como herramientas para determinar la idoneidad de iniciar el tratamiento de la osteoporosis en este momento.

4) Usando QUS para monitorear el tratamiento de la osteoporosis

En este momento, QUS no se recomienda para el monitoreo de la respuesta al tratamiento en pacientes con osteoporosis, tanto debido a la ausencia de ensayos clínicos aleatorizados, doblemente cegados y controlados con placebo (RCT) y la evidencia relativamente ambigua que se ha generado por los estudios que han sido publicados.¹⁴⁸⁻¹⁶⁴ Se ha observado que los cambios en los parámetros de QUS, especialmente el índice de rigidez (SI), imitan la respuesta al tratamiento observada en BMD. En dos estudios que involucraron alendronato, por ejemplo, el SI de Aquiles se observó que aumentaba significativamente con el tiempo.^{149,150} Claramente, sin embargo, se necesitan más RCT para determinar si los parámetros de QUS son lo suficientemente sensibles como para cambiar con el tratamiento, si los instrumentos de QUS son lo suficientemente sensibles como para detectar estos cambios, y si la precisión de estos instrumentos es tal que las medidas repetidas pueden realizarse sin un exceso de 'ruido'. Hay alguna evidencia de que la precisión del instrumento es adecuada en el corto plazo; pero ¿qué sucede a largo plazo? ¿Qué se puede decir sobre lo que se va a usar para monitorear el tratamiento, probablemente los dispositivos de talón serán los más exitosos, ya que las mediciones trabeculares parecen ser más precisas que las que se han logrado con cualquiera de los dispositivos corticales.

5) Caso de hallazgo

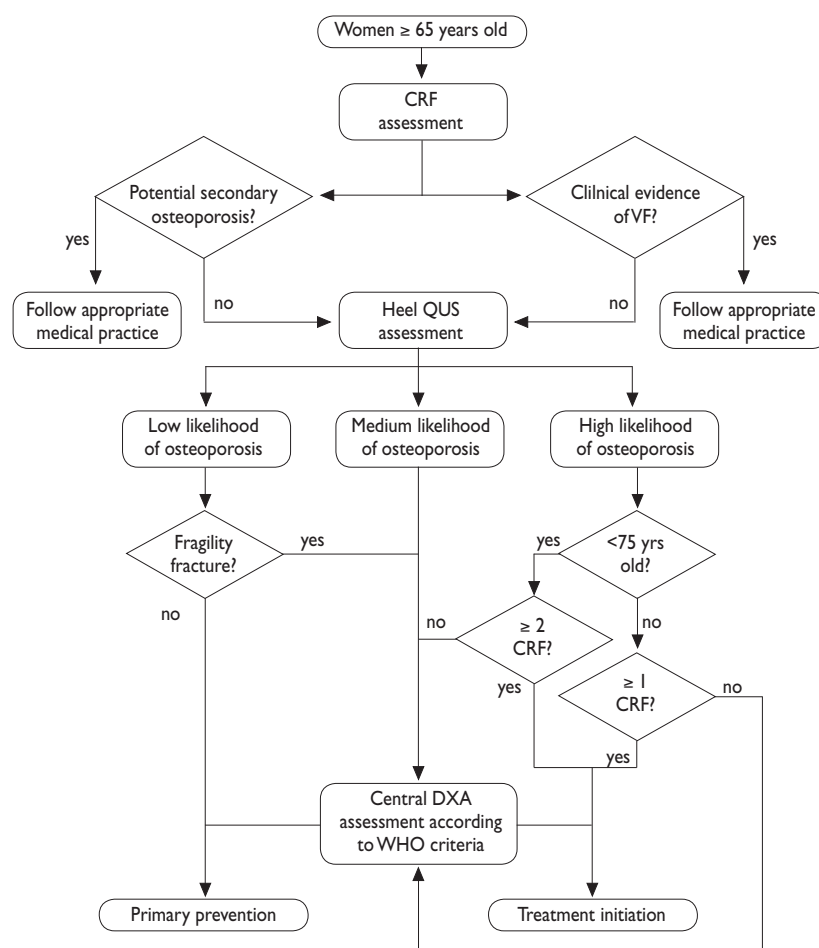
El hallazgo de casos implica distinguir a los sujetos en el mayor o menor riesgo de un trastorno, quienes por lo tanto no requieren más investigación porque su enfermedad

Table IV
CLINICAL RISK FACTORS FOR OSTEOPOROSIS
FOR USE WITH QUANTITATIVE ULTRASOUND

• Age over 75 years ^{132,133}
• Low BMI ($<20 \text{ kg/m}^2$) ^{132,134,135}
• Previous fragility fracture after the age of 50 ^{132,135,136}
• Maternal history of hip fracture ¹³⁷
• Current smoking ¹³⁸
• Diabetes
• No prior hormone replacement therapy (HRT) ¹³⁵
• Prior use of systemic glucocorticoids ^{135,139}
• Fall within the past 12 months ^{135,140}
• Use of arms to stand up 3 times from a chair (Missed Chair Test) ^{135,140,141}

status is reasonably well known, from subjects at intermediate risk whose disease status remains equivocal, thereby requiring further evaluation. At present, there is fair empirical support for the use of heel QUS for osteoporosis case finding among Caucasian and Asian females who are at least 65 years old. The evidence for the use of cortical devices is poor, and for males and other ethnic populations generally lacking altogether. Nonetheless, we feel that the proposed case-finding protocol depicted in figure 1 is reasonable for clinical practice, in terms of distinguishing individuals who require from those who do not require further evaluation of fragility fracture risk.

To begin, each patient would undergo an assessment to identify any clinical risk factors. Using this protocol, patients who are suspected to be at risk for secondary osteoporosis—for example, because of prolonged systemic use of corticosteroids—or who have a clinically-evident vertebral fracture would proceed directly to management deemed appropriate for their condition. All others would undergo a heel QUS. Based upon this, those whose QUS parameters suggest a low likelihood of future fracture would be assigned to receive primary prevention, unless they have had a fragility fracture, in which case they would undergo DXA BMD. Those for whom results indicate an intermediate risk of future



CRF= clinical risk factors; VF = vertebral fracture; QUS = quantitative ultrasound; DXA= dual-energy x-ray absorptiometry; WHO = World Health Organization

FIGURE 1. CASE-FINDING PROTOCOL

fracture, in that they lie between the upper and lower thresholds, also would undergo DXA BMD. And those patients for whom the risk of future fracture is deemed to be high, based upon the results of heel QUS, would proceed to treatment if they are ≥ 75 years old and have at least one other CRF besides age, or if they are < 75 and have at least two clinical risk factors. Otherwise, they too would proceed to DXA BMD.

The primary advantage of this protocol, especially in terms of cost, is that it saves performing costly and, sometimes relatively inaccessible DXA on all patients. In particular, those with a low risk of fracture by QUS would avoid DXA unless they have had a fragility fracture; and those with a high risk of fracture by QUS would avoid DXA if they have at least two CRF, counting age. As stated at the outset, this would have particular relevance in localities in which access to DXA is scarce or too costly to be performed, both of which likely apply to the majority of patients in many developing countries.

6) QUS quality assurance and quality control

Technically, quality assurance primarily deals with the performance of the equipment, whereas quality control is more heavily grounded in theory and statistics, emphasizing the quality of the actual test. For practical purposes, however, these two concepts often are treated as the same,¹⁶⁵ and this paper will not seek to further delineate them. The primary issues of importance are those of test/equipment accuracy, precision, and reproducibility. Accuracy is a measure of how close a provided answer or value is to the true answer or value.¹⁶⁶ If one were to visualize a game of darts, for example, darts that hit the bull's eye are said to be accurate. Precision, on the other hand, is a measure of consistency. If five darts are thrown, do they all end up close to each other (high precision) or widely spread (low precision)?¹⁶⁶ The two concepts, accuracy and precision, are not the same. One could have all one's darts bunched together far from the bull's eye (high precision, low accuracy); or one could have all one's darts widely spread, but all equidistant from the bull's eye, so that the average of their positions is near to the center dot (high accuracy, low precision). Reproducibility measures how well the same test done on the same person or sample yields the same result, whether the test is performed by the same technician (intra-observer) or a different technician (inter-observer).¹⁶⁶ These three parameters are important, whether a test is being performed to diagnose disease, monitor its course, or identify potential cases.

With heel QUS, there are several potential sources of *in vivo* measurement error, which include surround-

ing soft tissue and foot positioning;¹⁶⁷⁻¹⁷⁰ soft-tissue thickness,¹⁷¹⁻¹⁷³ temperature^{170,174} and composition; the quality of sound transmission from the coupling medium to the skin; and properties of the coupling medium between the transducers and the skin, whether it be a fluid bath or sound transmitting pads.^{167,170,175-178} One of the most important components of QA entails using some sort of test object, which can be either a standard or phantom,¹⁶⁵ to monitor instrument performance and make necessary calibrations when measurement accuracy begins to stray. A standard is an object of known acoustic properties, which does not necessarily resemble the anatomy of interest. Conversely, a phantom is designed to emulate the anatomy and acoustic properties that exist during *in vivo* measurements as much as possible. With respect to optimizing QUS device performance, phantoms are more useful. Unfortunately, no universally-applicable phantoms exist. Consequently, manufacturer-specific phantoms must be used, and measured each day that the respective device is used, following the manufacturer's protocol, to detect performance changes that may result from component aging or failure. Detection of these changes allows both for necessary repairs, and for adjustments to specific readings by applying a correction factor to patient data.¹⁷⁷ Table V provides a brief list of important guidelines regarding quality assurance and control:

Summary

To date, no satisfactory evidence exists either supporting or refuting the usefulness of quantitative ultrasound in Latin populations, so that further research clearly is warranted. Nonetheless, there is enough evidence in other populations to suggest that QUS may be an acceptable, low-cost and readily-accessible alternative to DXA measurements of BMD in the management of osteoporosis in Hispanics. Many different QUS devices exist that are quite different in terms of the parameters they measure and the strength of empirical evidence supporting their use. In general, heel QUS appears to be most tested and most effective. Some, but not all heel QUS devices are effective assessing fracture risk in some, but not all populations, the evidence being strongest for Caucasian females > 55 years old, though some evidence exists for Asian females > 55 and for Caucasian and Asian males > 70 . Certain devices may allow for the accurate diagnosis of osteoporosis, but very limited evidence exists supporting the use of QUS use during the initiation or monitoring of osteoporosis treatment. A reasonable protocol for osteoporosis case-finding relies upon the combined assessment of clinical risk factors and heel QUS. However, monitoring and maintenance of test and

Table V
RECOMMENDATIONS FOR QUALITY ASSURANCE/QUALITY
CONTROL IN QUS SYSTEMS

- (1) QUS-specific information and training must be provided prior to measuring patients in routine clinical practice;
- (2) To assist in optimizing QUS measurements, in vivo precision error should be calculated by each QUS facility's technologist, in accordance with ISCD recommendations for DXA, rather than relying upon precision values reported in the literature or by the manufacturer; once measurement precision is known, it is possible to determine the minimal detectable difference between two measurements that is statistically significant;
- (3) Obtaining facility accreditation for QUS is recommended;
- (4) As with other methods, with QUS, anatomically-consistent regions of the bone must be measured to enhance accuracy, and precision is affected by the quality of sequential repositioning of each patient; the use of an imaging system may help to overcome positioning errors by placing a region of interest (ROI) on the image;¹⁷⁹
- (5) Attempts should be made to maintain a relatively-constant and standard temperature for all readings; and when an aberration is felt to exist because of temperature, accommodation should be made and the measurement repeated; for example, with heel measurements, a cold foot can falsely lower SOS measurements; hence, if the SOS result is low and this value clinically-important, the foot should be warmed and the measurement repeated;
- (6) Oedema of the foot can significantly affect heel QUS readings, so that this test should not be performed in such patients;
- (7) Achieving good-quality coupling of the ultrasonic beam as it passes into the body is essential; a coupling gel or liquid must be used with all methods to ensure proper penetration through the skin;
- (8) Manufacturer-specific phantoms must be measured each day a device is used, following the manufacturer's protocol, to detect equipment changes that may result from component aging or failure, and thereby allow for necessary repairs, or for adjustments to specific readings by applying a correction factor to patient data;¹⁷⁷
- (9) It generally is accepted that long-term stability and precision errors detected during phantom measurement should not exceed ¼ T-score to restrict misclassification errors to within a clinically-acceptable level¹¹⁹
- (10) Each facility should periodically assess the performance of its technologists; two essential components of this are (1) ensuring that adequate time is utilized performing measurements; and (2) measuring intra-observer reliability to generate a coefficient of variation (CV); the in vivo CVs generally quoted in the literature range from 0.8 - 5 % and 0.2 - 1 % for BUA and SOS, respectively.

instrument accuracy, precision and reproducibility are paramount to the effective clinical use of QUS. And, as stated earlier, there is a huge call for further research in non-Caucasian, non-Asian populations.

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