REVIEW

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Uses and misuses of quantitative ultrasonography in managing osteoporosis

ABSTRACT

Quantitative ultrasonography is attractive as a test for osteoporosis, being precise, radiation-free, portable, and inexpensive, but it is still no substitute for the gold-standard test, dual-energy x-ray absorptiometry (DXA). At present, it cannot be used to diagnose osteoporosis or to monitor the effects of medications on bone density. As more data become available, however, it may play a larger role. A thorough understanding of the utility and limitations of this test is necessary for using it effectively in clinical practice.

KEY POINTS

Quantitative ultrasonography measures the speed and attenuation of sound in bone; the higher these values, the stronger the bone. It can also give an estimate of bone mineral density, but not an actual measurement.

This test can give an accurate estimate of the risk of fracture in postmenopausal women and older men and is useful in education programs to increase public awareness of osteoporosis.

In theory, quantitative ultrasonography could be useful for prescreening healthy postmenopausal women and older men to determine if a DXA scan is needed.

T scores obtained by quantitative ultrasonography are different than T scores derived by DXA and cannot be used with the World Health Organization classification of bone mineral density to diagnose osteoporosis.

QUANTITATIVE ULTRASONOGRAPHY seems at first glance to be a good alternative to dual-energy x-ray absorptiometry (DXA), the gold standard for diagnosing osteoporosis, predicting fracture risk, and monitoring therapy. It is less expensive than DXA, the equipment is portable, and it does not use ionizing radiation.

However, despite its advantages, this test is not yet a substitute for DXA for diagnosing and classifying osteoporosis nor for monitoring therapy. The various ultrasound devices are not comparable to one another, quality assurance and instrument calibration are uncertain, standardized reference databases are lacking, and we do not have enough data to correlate ultrasonographic measures with clinical risk factors for fracture.

This article explains how quantitative ultrasonography works, evaluates how it compares with DXA, and explores its possible clinical applications (**TABLE 1**). We present cases that demonstrate how it should and should not be used at this point.

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OSTEOPOROSIS IS COMMON AND SERIOUS

Osteoporosis is characterized by compromised bone strength due to both low bone density and poor bone quality.[1]

About 30% of white women[2] (the most studied group) and 19% of men[3] age 50 and older have osteoporosis. If we consider both osteoporosis and osteopenia (a less-severe category of low bone density), the percentage of people age 50 or older with either of these conditions is 55%.[4] About 44 million American men and women have either osteoporosis or osteopenia.[4]

By age 50, a white woman has about a 40% lifetime risk of a fracture of the hip, spine, or distal forearm, and a white man of this age has a 13% risk.[5] Fractures of the spine and hip increase the risk of chronic pain, deformity, depression, disability, and death. About half of patients who suffer a hip fracture never walk again without assistance, and 25% need long-term care.[6] A hip fracture or clinical vertebral fracture increases the risk of death by about 20% over the following 5 years;[7] mortality rates are higher in men than in women, even after adjusting for age.[8]

DXA IS THE GOLD STANDARD

DXA is the gold standard for diagnosing osteoporosis,[9] for predicting fracture risk,[10] and for monitoring changes in bone mineral density in response to therapy.[11]

Osteoporosis is diagnosed using the classification system of the World Health Organization.[12] In a patient who has never had a fragility fracture, osteoporosis is defined as bone mineral density at least 2.5 standard deviations (SD) below the mean of a young adult reference population, a scoring system called a T score.[13]

Bone mineral density is measured in the lumbar spine, total proximal femur, femoral neck, and "33% radius" (also called the one third radius, an area defined as being within lines drawn 10 mm proximal and 10 mm distal to a point that is one third the distance from the distal to the proximal end of the ulna; the ulna is used as the landmark for the radius because it is easy to measure).

TABLE 1

Clinical applications of quantitative ultrasonography

Uses
- To assess fracture risk when dual-energy x-ray absorptiometry (DXA) is not available or affordable
- As part of a skeletal-health education program

Misuses
- When it is unlikely to influence clinical decisions
- For diagnostic classification of osteoporosis
- In patients who have already had a DXA study
- To monitor response to therapy

Potential future uses (much more data required)
- To quantify fracture risk when combined with clinical risk factors
- For diagnostic classification of osteoporosis
- To select patients likely to benefit from medications
- To monitor response to therapy

DXA has disadvantages

DXA uses ionizing radiation, and the machines are large and expensive—some cost more than $100,000. A device that could reliably perform the same or similar functions without ionizing radiation, at a lower cost, and with greater portability would be highly desirable.

Many non-DXA technologies for evaluating skeletal health have been developed. Of these, quantitative ultrasonography is the most widely used in clinical practice. But to use this test effectively, one must understand the technology and the implications of measurements for patient care.

By age 50, a white woman has about a 40% lifetime risk of a fracture

HOW QUANTITATIVE ULTRASONOGRAPHY WORKS

Ultrasonography has been used to characterize properties of bone for more than 50 years.[14] In 1984, a landmark study showed that it could distinguish between elderly women with and without a history of hip fracture.[15] Since then, numerous studies have shown that it predicts fracture risk.[10,16–20]

The US Food and Drug Administration first approved a quantitative ultrasound device for commercial use in 1998; today, a plethora of devices are available in the United States and worldwide (FIGURE 1).

The devices use high-frequency sound waves, typically between 0.1 and 1.0 MHz,

Quantitative ultrasonography of the heel

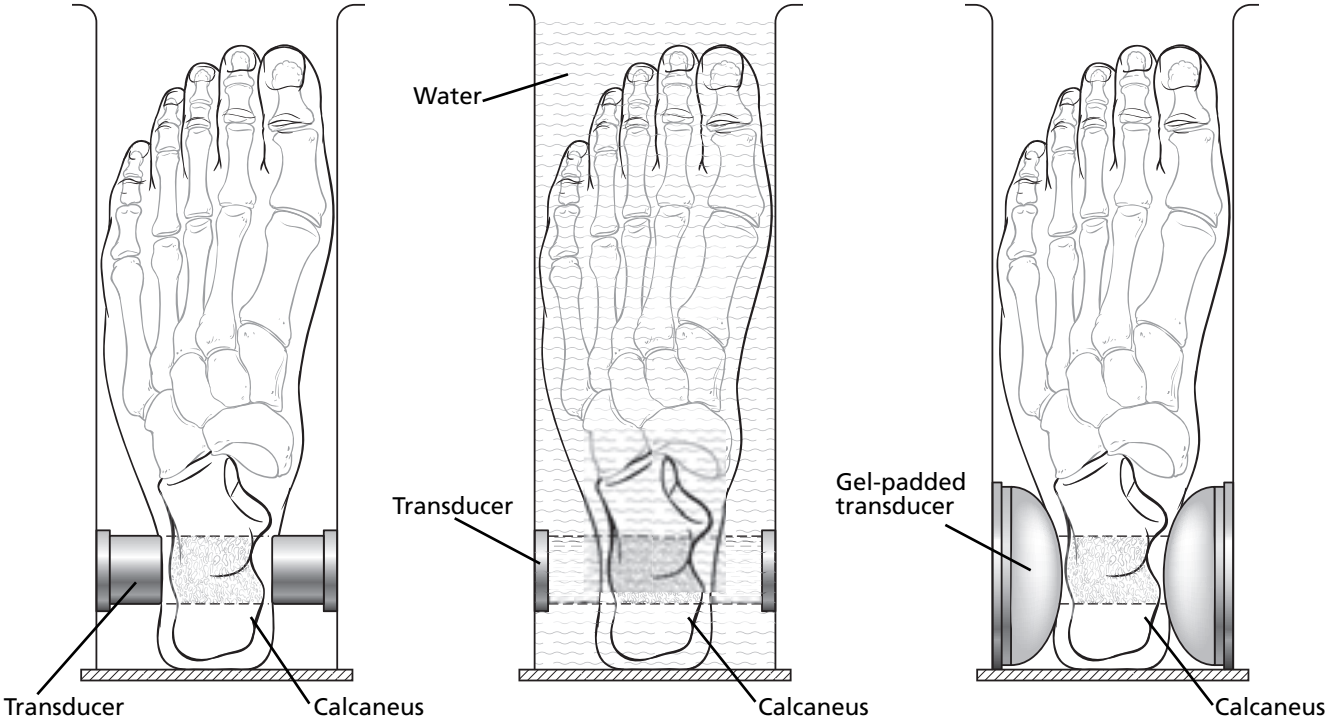

FIGURE 1. Quantitative ultrasonography of the heel. Some devices bring the transducers into contact with the foot (left), others use a water bath to transmit sound waves (center). Another type of device uses gel-padded transducers (right).

which are produced and detected by highly efficient piezoelectric transducers. The transducers must make good acoustical contact with the skin over the bone being tested, which is achieved by "wet" methods (eg, a water bath), "dry" methods (eg, silicone pads, ultrasound gel), or a combination of these methods.

The technical differences among machines are great: different ones use different frequencies, have different-sized transducers, and sometimes measure different regions of interest, even at the same skeletal site. The calcaneus is the area most often tested, although other bones can be used, including the radius, tibia, and finger phalanges.

What quantitative ultrasonography measures

Commercial systems usually measure two variables: the speed of sound and broadband ultrasound attenuation.

The speed of sound through bone varies according to the type of bone, typically ranging from 3,000 to 3,600 m/second in cortical bone and from 1,650 to 2,300 m/second in trabecular bone.[21]

Broadband ultrasound attenuation is a measure of the loss of energy, or attenuation, of sound as it passes through bone, reported in decibels per megahertz (dB/MHz).

The higher these values, the higher the bone density. Different companies have developed proprietary indices based on these values, such as the "quantitative ultrasound index" with the Hologic Sahara system or the "stiffness index" with the General Electric Healthcare Achilles Express system.

T scores are not equal as measured by ultrasonography and DXA

The speed of sound and broadband ultrasound attenuation can be used to *estimate* bone mineral density and a T score, but an ultrasound

A premenopausal woman with a low T score by ultrasonography

A healthy 32-year-old premenopausal woman with a family history of osteoporosis presents after having had a quantitative ultrasonographic measurement of the heel at a health fair. Her report shows an estimated bone mineral density T score of –1.5. What should be done?

DISCUSSION

A T score of –1.5 is compatible with a diagnosis of low bone mass (osteopenia) according to the World Health Organization classification of bone mineral density. However, this standard does not apply to premenopausal women; to skeletal sites other than the spine, hip, or forearm; or to technologies other than DXA. Therefore, a diagnosis of low bone mass or osteopenia cannot be made.

Low ultrasonographic measurements correlate with increased fracture risk in postmenopausal women, but the relationship is not well established in premenopausal women. Even if the relative risk of fracture is higher for this patient than for a woman of the same age with an ultrasound T score of 0.0, the 10-year probability of fracture is likely very low.

This patient should be advised that she probably has a below-average bone mineral density due to low peak bone mass; that the probability of fracture is low; that her bone mineral density is likely to remain stable until she becomes perimenopausal; and that treatment should consist of a healthy lifestyle, ie, regular weight-bearing exercise, adequate daily calcium and vitamin D, and avoiding cigarette smoking and excessive alcohol intake.

Pharmacologic therapy is not indicated for this patient. Whether to investigate for factors contributing to her probably less-than-average bone mineral density should be based on her and her physician's level of concern.

T score cannot be compared with a DXA T score because these technologies measure different properties of bone and use different reference databases. Although most of what quantitative ultrasonography measures is related to bone mineral density,[22] it also likely measures properties of bone strength independent of bone mineral density.[23,24]

"Accuracy" or "trueness"—the correlation between measured bone mineral content (usually expressed in grams) and the actual bone mineral content obtained by incinerating a bone specimen and weighing the remaining bone ash—is not applicable to quantitative ultrasonography because it does not measure bone mineral content. Radiographic studies such as DXA do measure bone mineral content and have an acceptable error of 5% to 15%.[25]

HOW CLINICALLY USEFUL IS QUANTITATIVE ULTRASONOGRAPHY?

How clinically useful is quantitative ultrasonography? The answer can be approached by examining its performance in each area that DXA is used: diagnosing osteoporosis, predicting fracture risk, and monitoring changes over time (TABLE 1).

Ultrasound estimates bone density, but does not actually measure it

Not for diagnosing osteoporosis

As stated previously, the World Health Organization criterion for the densitometric diagnosis of osteoporosis is a T score of –2.5 or less in the hip, spine, or forearm, as measured by DXA. The rationale for using this threshold is that it identifies about 30% of postmenopausal white women as having osteoporosis—very roughly the same figure as the lifetime risk of fracture in this population. Since the relationship between osteoporosis prevalence and fracture risk is not the same if bone mineral density or other characteristics of bone strength are measured at other skeletal sites with non-DXA devices, quantitative ultrasonography cannot be used to diagnose osteoporosis.[26]

T scores decline with age, but by different amounts in different skeletal sites and using different measurement technologies.[27,28]

A postmenopausal woman with a low T score by ultrasonography

A 71-year-old woman has a screening quantitative ultrasonographic measurement of the heel that is reported as a T score of –2.6. What is her diagnosis and what should be done?

DISCUSSION

Quantitative ultrasonography cannot be used for diagnostic classification, but the low T score suggests that she has an increased risk of fracture and she should be further evaluated. She should next have a DXA scan of the spine and hip to establish a diagnosis, which is likely to be osteoporosis. She should also have laboratory evaluation to look for contributing factors.

In addition to recommendations for exercise, fall prevention, calcium, and vitamin D, pharmacologic therapy is probably indicated and can be expected to reduce fracture risk by approximately 50%. A follow-up DXA scan in 1 to 2 years may help in assessing her response to therapy. A stable or increased bone mineral density is acceptable, but a further reduction warrants more aggressive treatment.

Quantitative ultrasonography plays no further role in this patient's management provided that DXA is available for diagnosis and monitoring.

A possible screening strategy: ultrasound for all, DXA for those with abnormal results

Although the coefficients of variance between ultrasonography and DXA at the same skeletal sites have been found to be as high as 0.8 and 0.9, ultrasonographic measurements at peripheral skeletal sites do not correlate with DXA measurements at central sites sufficiently to allow quantitative ultrasonography as a substitute for DXA for diagnostic testing.[29]

Can predict fracture risk

Many studies have shown that quantitative ultrasonography of peripheral skeletal sites can help predict fracture risk in postmenopausal women and older men.

The risk of fracture is usually expressed as the relative risk or odds ratio for patients with ultrasonographic values 1 SD below the mean. There is a gradient of risk: the more SDs below the mean in speed of sound, broadband ultrasound attenuation, or estimated bone mineral density, the greater the risk.

Marshall et al[10] performed a meta-analysis of DXA studies and calculated that if the bone mineral density in the hip is 1 SD below the age-adjusted mean, the relative risk of hip fracture is 2.6.

The numbers are similar for ultrasonographic measurements. In the French Épidémiologie des Ostéoporoses (EPIDOS) prospective observational study,[23] in 5,662 elderly women (mean age 80.4 years), if the speed of sound in the calcaneus was 1 SD below the mean, the relative risk of hip fracture was 1.7 (95% confidence interval [CI] 1.4–2.1). If the broadband ultrasound attenuation was 1 SD below the mean, the relative risk was 2.0 (1.6–2.4). With DXA, if the bone mineral density at the femoral neck was 1 SD below the mean, the relative risk was 1.9 (1.6–2.4).

In the Study of Osteoporotic Fractures[17] (SOF), a prospective observational study of 6,189 women older than 65 years, each 1-SD reduction in broadband ultrasound attenuation at the calcaneus was associated with an increase in the relative risk of fracture of 2.0 (1.5–2.7), compared with 2.6 (1.9–3.8) for a 1-SD reduction in bone mineral density at the femoral neck.

The National Osteoporosis Risk Assessment (NORA)[30] was the largest prospective observational fracture study, with 200,160 women age 50 years and older with no previous diagnosis of osteoporosis. In a subset of 7,562 women who underwent quantitative ultrasonography of the calcaneus, the relative risk for a hip fracture for a 1-SD reduction of estimated bone mineral density (using the manufacturer's proprietary young-adult reference database) was 1.28 (0.86–1.90). Relative risk was similar for younger and older postmenopausal women: 1.24 (1.0–1.6) for

A postmenopausal woman with a fragility fracture

A 54-year-old woman who is postmenopausal and estrogen-deficient trips and falls when walking to the mailbox and fractures her distal radius. She presents to you for follow-up after usual care by an orthopedic surgeon. Because of your interest in osteoporosis, you are anxious to use the quantitative ultrasonography device you recently purchased: her heel has a T score of –1.8. What should be done next?

DISCUSSION

A fragility fracture is sufficient to clinically diagnose osteoporosis. A distal radius fracture suggests an increased risk of future fractures, and an ultrasonographic T score provides no additional information in this case.

DXA of the spine and hip may help guide therapy and serve as a baseline for future comparison. The patient should be medically evaluated for factors contributing to bone fragility, and nonpharmacologic and pharmacologic therapy to reduce the risk of future fractures should be strongly considered.

women age 50 to 64 years and 1.57 (1.3–1.9) for women age 65 to 99 years.[31]

Quantitative ultrasonography can also predict fracture risk in men. The Epidemiological Study on the Prevalence of Osteoporosis (ESOPO),[32] in 4,832 Italian men age 60 to 80 years, found an odds ratio for hip fracture for a 1-SD reduction of speed of sound of 1.71 (1.18–3.24); for broadband ultrasound attenuation the number was 2.24 (1.61–3.08).

Quantitive ultrasonography has been shown to predict fractures even if performed on machines made by different manufacturers,[33,34] or at sites other than the heel.[35,36] It can also predict fragility fractures in sites other than the hip.[37,38]

Possible use as prescreening for DXA scanning

A possible use for quantitative ultrasonography is in screening to determine whether osteoporosis is likely to be present and whether further evaluation is needed. This strategy may enable more people to be screened at a lower cost. Patients with an ultrasonographic measurement below a given threshold would be advised to undergo DXA for diagnostic classification and to establish a baseline for monitoring response to therapy. Patients with values above the threshold could be reassured that they probably do not have low bone mineral density and that no further investigation is warranted.

Unfortunately, differences in machines, reference databases, reported characteristics, and skeletal sites measured make it impossible to establish universal screening thresholds. Device-specific thresholds depend on the selected levels of sensitivity and specificity. In addition, cost-effectiveness analyses of this strategy have yielded mixed results.[39,40]

More data are needed to develop strategies for using quantitative ultrasonography effectively for screening. **TABLE 2** provides our personal recommendations; these apply to postmenopausal women and older men—the relationship between quantitative ultrasonographic measurements and fracture risk is not well established for premenopausal women and young men.

The heel responds more slowly to therapy than the spine

All patients with a fragility fracture or who are at high risk for fracture should be considered for measurement of bone mineral density by DXA, regardless of the results of quantitative ultrasonography. Risk factors for fracture include advanced age, parental history of hip fracture, cigarette smoking, and long-term glucocorticoid therapy. If DXA is unavailable or unaffordable, treatment to prevent fractures should be considered for patients with a quantitative ultrasonographic T score of –1.0 or lower.

The Bone Mass Measurement Act of 1998 allows Medicare reimbursement for DXA "for a confirmatory baseline bone mass measurement" following a quantitative ultrasonographic measurement, with no time interval restriction, for the purpose of monitoring bone mineral density with DXA.[41]

Determining who needs therapy

In almost all of the large randomized clinical trials of drug therapy for osteoporosis, patients

TABLE 2

Recommendations for bone mineral testing by DXA following quantitative ultrasonography

ULTRASONOGRAPHIC T SCORE	RISK OF OSTEOPOROSIS	IS DXA NEEDED?
≥ +1.0	Low	No—unless risk factors are present
between +1.0 and –1.0	Intermediate	Yes—for diagnostic classification and baseline for therapy
≤ –1.0	High	Yes—for diagnostic classification and baseline for therapy

DXA, dual-energy x-ray absorptiometry

were selected on the basis of bone mineral density measurements with DXA, with or without clinical risk factors.

Ultrasonography may help identify patients at high risk of fracture. Whether treating such patients reduces risk has not been established, but given the limited access to DXA in some places, treatment strategies based on quantitative ultrasonography would be an attractive option.

Ultrasound is increasingly being used at pharmacies, shopping centers, and health fairs

Monitoring response to treatment

Tests used in monitoring therapy should:

- Be precise (ie, they should give consistent results over time when there has been no real change)
- Be responsive (ie, they should show a change if there actually has been a change, and in a clinically useful period of time)
- Correlate well with clinical outcomes (ie, reduced fracture risk).

DXA is very precise but not very responsive (more so in some skeletal sites than others).[11] In contrast, measurements of markers of bone turnover are not very precise but more responsive,[42] and therefore sometimes as useful.

In general, quantitative ultrasonography is fairly precise in the short term, but the precision varies widely among devices and whether speed of sound or bone ultrasound attenuation is measured. In a comparison of six devices,[33] the short-term precision was comparable to that of DXA.[43]

As for responsiveness, the least significant change at the 95% level of confidence, which is the smallest change that is considered to be statistically significant, is calculated by multiplying the precision error by 2.77.[11] The monitoring time interval (ie, the time required to detect a significant change) is calculated by dividing the least significant change by the expected change per year. Since the changes in bone mineral density in response to therapy are usually less at peripheral skeletal sites (eg, the calcaneus) than at central sites (eg, the lumbar spine), the monitoring time interval is likely to be longer for peripheral skeletal sites. Therefore, testing peripheral skeletal sites is less useful clinically.

Using DXA of the lumbar spine, the recommended monitoring interval after starting medications is about 1 to 2 years.[11] Using quantitative ultrasonography of the calcaneus, the monitoring time interval is two to three times longer.[44] A test that takes many years to change significantly is impractical for monitoring the effect of therapy. Nevertheless, monitoring with quantitative ultrasonography at some skeletal sites[45] could have a role in specific clinical situations, such as when DXA is unavailable or unaffordable.

An increase in bone mineral density in response to therapy, measured by DXA, correlates with reduced fracture risk,[46] but to what extent has been debated.[47] We know of no analogous data for quantitative ultrasonography.

Useful in health education

Quantitative ultrasonography devices are increasingly being used at pharmacies, shopping centers, and health fairs, often with long lines of visitors waiting to be tested. The pop-

ularity of this test is testimony to our innate desire to learn more about ourselves. Perhaps more valuable than actual test results is the opportunity to educate the public on the importance of regular weight-bearing exercise and adequate daily intake of calcium and vitamin D.

Other clinical factors

Quantitative ultrasound machines are much cheaper to buy and operate than are DXA machines. Reimbursement for an ultrasound test in the United States is typically about one third the cost of a DXA scan. The small size, portability, and ease of use of the machines are distinct advantages of quantitative ultrasonography (TABLE 3). Because ionizing radiation is not used, it is not necessary to meet radiation safety requirements or to have a trained radiology technician perform the test, as is required for DXA in some states.

Although the role of quantitative ultrasonography in clinical practice has not yet been fully established, suggestions for its appropriate use are listed in TABLE 3.

TABLE 3

Comparison of quantitative ultrasonography and DXA

FACTOR	QUANTITATIVE ULTRASONOGRAPHY	DXA
Uses ionizing radiation	No	Yes
Is small and portable	Yes	No
Is low-cost	Yes	No
Can diagnose osteoporosis	No	Yes
Can predict fracture risk	Yes	Yes
Can monitor therapy	No	Yes

DXA, dual-energy x-ray absorptiometry

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