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Original Article

North American Male Reference Population for Speed of Sound in Bone at Multiple Skeletal Sites

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Abstract

Alternatives to dual-energy X-ray absorptiometry (DXA) have been sought to increase access to low-cost osteoporosis risk assessment. Early quantitative ultrasound (QUS) systems measured speed of sound (SOS) and broadband ultrasound attenuation (BUA) at the calcaneus, and these were demonstrated to be good predictors of hip fracture risk. Recent studies have demonstrated the usefulness of other peripheral sites to assess bone status. The Sunlight Omnisense™ (Sunlight Medical, Rehovot, Israel) is a portable, inexpensive QUS device capable of multiple-site SOS measurement. To provide a robust male reference database, 588 healthy Caucasian males aged 20–90 yr were recruited from 6 centers across North America. SOS measurements were taken at the distal 1/3 radius, proximal third phalanx, midshaft tibia, and fifth metatarsal. A female reference database has previously been collected at North American sites. The results indicate that SOS in males exhibits an age-related decline beginning in the fifth decade at the radius, phalanx, and metatarsal, whereas the tibial SOS remains nearly constant until the ninth decade. Although females reach a higher-peak SOS than males at most sites, SOS is higher in males at all sites after the sixth decade, as a result of a more gradual decline in SOS. Longitudinal monitoring of healthy men should be performed to confirm these cross-sectional results.

Key Words: Quantitative ultrasound; multiple sites; speed of sound; reference data.

Introduction

Recently, an increasing senior population and greater public awareness of osteoporosis has caused a boom in bone measurement in North America *(1–4)*. Dual energy X-ray absorptiometry (DXA) has long been considered the gold standard for measurement of osteoporosis and other bone diseases. The advantages of DXA are its precision, low radiation dose, and ease of use *(5,6)*. DXA is also advantageous because it can measure specific fracture risk sites (hip and spine) or the entire body. Despite these benefits, new technologies, including quantitative ultrasound (QUS), have

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been developed as primary public screening tools for the assessment of fracture risk *(5,7–11)*. QUS systems have obvious practical advantages over DXA, including portability, low cost, the absence of ionizing radiation, and less operator training *(8)*. There are also some less obvious advantages to using QUS for osteoporosis screening. SOS measurements have the potential to predict fracture better than BMD alone, because the ultrasonic wave is influenced by both density and structural properties of the bone *(12–17)*; however, the ability of QUS devices to reflect bone structure *in vivo* is still speculative. The use of nonspecific skeletal sites to predict global fracture risk has been established, permitting measurement at sites other than the hip and spine *(18–23)*. QUS is also an especially valuable tool for men, because BMD of the lumbar spine, as measured by DXA, is often falsely elevated over the age of 65 as a result of degenerative changes such as osteophytes, facet joing arthritis, spinal fusion, and aortic calcification *(5,6,24,25)*. The many advantages of this technology have led to an explosion of new QUS devices on the market in the last decade.

Prior to clinical interpretation of SOS measurements with any new device, the age-dependent pattern of bone loss (indicated by SOS) for adults must be clearly established. Although longitudinal monitoring of a population would be preferred, the initial step in collecting reference data entails measuring SOS in a cross-sectional sample of healthy adult volunteers to determine peak bone mass attainment and subsequent changes with age.

The Sunlight Omnisense™ Bone Sonometer (Sunlight Medical, Rehovot, Israel) is a noninvasive QUS device that measures SOS along the length of a long bone. The technique is not affected by thickness of subcutaneous tissue and, unlike other QUS systems, is capable of measurement at multiple (peripheral) skeletal sites. Ultrasonic waves are emitted from one end of a hand-held probe, transmitted through the outer layer of a long bone, and received at a transducer at the other end of the probe. Differences in SOS probably reflect differences in the biological properties of the cortical bone, with decreased SOS likely the result of increased cortical porosity, cortical thinning, or the presence of unmineralized bone. Measurement precision is ensured by software, which requires concordance of three to five serial measurements as the probe is rotated around the long axis of the bone.

Table 1
Study Enrollment Information

	N
Sites	
All sites	592
Bangor, ME, USA	94
Vancouver, BC, Canada	110
San Francisco, CA, USA	101
Hamilton, ON, Canada	89
Saskatoon, SK, Canada	96
Portland, OR, USA	102
Reasons for ineligibility:	
Age out of range	1
No measurement (any of four skeletal sites)	3
Total ineligible	4
Total eligible for study	588
No radius measurement	31
Total eligible for the radius study	557
No tibia measurement	10
Total eligible for the tibia study	578
No metatarsal measurement	65
Total eligible for the metatarsal study	523
No phalanx measurement	4
Total eligible for the phalanx study	584

In this study, we have documented the SOS at four skeletal sites in healthy North American Caucasian men, aged 20–90. A female database has been established previously *(26)*. The reference data will be used to determine the pattern of attainment of peak SOS values and subsequent changes with aging.

Materials and Methods

Subjects

A convenient sample of subjects was recruited in six North American cities using advertisements placed in newspapers, churches, community centers, places of business, and nursing homes. Five hundred eighty-eight healthy Caucasian males (mean age: 50.6 ± 17.8 yr; range: 20–90) were eligible for the study, out of 592 that were measured. Complete study enrollment information is available in Table 1. The four excluded men were ineligible because they were outside the age range, or no measurements were successfully performed. Many possible participants were also eliminated from consideration before a measurement was

attempted, because of the following exclusion criteria. None of the eligible subjects had a history of osteoporotic fracture or a chronic condition affecting bone metabolism such as hyperparathyroidism, diabetes mellitus, hyperthyroidism, inflammatory arthritis, and endogenous or iatrogenic glucocorticoid excess or malabsorption. No subject had been exposed for more than 1 yr within the preceding 3 yr to a medication affecting bone, such as anticonvulsants, immunosuppressants, chemotherapeutics, GnRH analogs, testosterone, steroids, androgen antagonists, bisphosphonates, calcitonin, or fluoride. All volunteers gave informed, written consent. Ethics approval was obtained at each of the six institutions that participated.

Demographic details of the study population are provided in Table 2. Most of the participants had lived in urban areas for the previous 20 yr (79.8%) and most of the men were born in North America (81.8%). A further 13.6% of the men were born in Europe, with 4.6% born elsewhere. The subjects' mean calcium intake was 1241 ± 749 mg/d.

Table 2
Demographic Characteristics of the Study Population

	N (%)
Age (yr)	
20–29	89 (15.1)
30–39	99 (16.8)
40–49	97 (16.5)
50–59	105 (18.4)
60–69	99 (16.8)
70–79	62 (10.5)
80–90	34 (5.8)
Total	588 (100.0)
Mean±SD	50.6±17.8
Range	20–90
Physical activity	
Seldom/never	45 (7.7)
Once/week	71 (12.1)
Several/week	275 (46.8)
Daily	196 (33.3)
Total	588 (100.0)
Body mass index (kg/m^2)	
≤ 25	208 (35.3)
26–30	272 (46.3)
31–35	77 (13.1)
35+	31 (5.2)
Total	588 (100.0)
Mean±SD	27.4±4.7
Range	18–64
Alcohol consumption	
Never	78 (13.3)
Past	62 (10.5)
Current	448 (76.2)
Total	588 (100.0)
Smoking	
Never	369 (62.8)
Past	149 (25.3)
Current	70 (11.9)
Total	588 (100.0)

Device Description

The Sunlight Omnisense Bone Sonometer measures the speed of conduction through bone of inaudible high-frequency acoustic waves produced at a frequency of 1.25 MHz by two signal generators in a hand-held probe. The same probe contains two different transducers such that the speed of conduction of the sound waves (SOS) that travel along the length of long bones can be measured using the "critical angle" concept *(27,28)*. Briefly, the transducer generates an array of ultrasound waves that move through the soft tissues and enter bone. On reaching the bone surface, the sound waves are refracted and their direction of propagation changes. Those waves that enter at a "critical angle" will be refracted such that their subsequent direction of travel through the bone is along its long axis. The receiver detects a small fraction of the original beam and the first waves to be detected are used to calculate the SOS. In clinical use, the SOS value generated is compared to a young adult and an age-matched population to generate T- and Z-scores, respectively.

Measurements

Speed of sound measurements were made in each volunteer at the distal 1/3 of the radius, the proximal phalanx of the third finger, the fifth metatarsus, and the midshaft of the tibia of the nondominant limb. In all cases, the probe was positioned in the direction of the long axis of the bone and good acoustic coupling was achieved with a thin layer of ultrasound gel.

Results

The precision and reproducibility of the Omnisense was previously established by Drake et al. dur-

Table 3
Mean SOS (in m/s) in Males by Decade at Four Skeletal Sites

	Radius			Tibia			Phalanx			Metatarsal		
Age	*N*	Mean SOS	SD	*N*	Mean SOS	SD	*N*	Mean SOS	SD	*N*	Mean SOS	SD
20–29	47	4081	120	48	3982	131	48	3971	150	44	3740	288
30–39	46	4108	123	47	3988	116	47	3943	193	44	3735	223
40–49	44	4117	109	44	3978	98	44	3971	192	41	3740	213
50–59	54	4071	139	54	3986	115	53	3933	162	50	3751	280
60–69	46	4043	134	49	3969	128	50	3891	176	44	3712	258
70–79	25	4006	134	28	3994	131	28	3825	244	21	3593	213
80–90	21	4030	124	20	3929	152	21	3786	189	15	3528	328

ing the collection of the female reference database *(26)*. Duplicate measurements (with repositioning) were performed at each anatomical site on 15 volunteers (10 premenopausal and 5 postmenopausal women) by 3 separate operators. Overall precision (including interobserver and intraobserver precision) was calculated for all six measurements taken at each site in each volunteer, in an attempt to quantify precision in a clinical setting. Precision was expressed as a coefficient of variation (CV = 0.4–0.82% for the four sites). To correct for bias in the CV resulting from the large SOS numbers, precision was also expressed as a standardized coefficient of variation (SCV = 1.5–2.7% or 3.0–4.5%, depending on the method of calculation used).

Mean SOS measurements by decade and according to site are given in Table 3. Moving-average plots of the male reference data were generated for each measurement site to show a smoothed progression of SOS with age. These plots of the male reference data are shown in Fig. 1. The curve for the tibia appears to be nearly horizontal from the age of 20 to 80, at which point SOS begins to decrease. The moving-average SOS of the other three sites increases to a peak between the ages of 42 and 46, with an overall plateau between 30 and 50 yr. Thereafter, SOS at the radius, phalanx, and metatarsal declines. After the age of 60, the SOS can be fitted to a linear regression at the phalanx and metatarsal sites ($p<0.03$ and $p<0.0005$, respectively).

Moving-average plots, including both male and female reference data, are shown in Fig. 2. The male SOS at the tibia remains higher than female SOS at the tibia throughout life ($p < 0.01$). At the other three sites, female SOS is higher from age 20 to 39, with a significant difference between male and female SOS at the radius and phalanx ($p < 0.0001$). Between the ages of 45 and 59, the radius, phalanx, and metatarsal SOS declines in females (–10.4 to –22.9 m/s/yr; mean = –15 m/s/yr) at a greater rate than in males (+1.5 to –7.7 m/s/yr; mean = –3 m/s/yr), and the reference curves cross. An interactive regression model was fitted to all reference data for ages 40–69, and the slope of the reference curve for men and women was found to be significantly different at all measurement sites in this age range ($p < 0.0001$). Female SOS remains lower than male SOS for the remainder of life at the radius, phalanx, and metatarsal.

Analysis was also performed to determine what effects, if any, known lifestyle and demographic variables had on SOS measurements. No significant relationships were found across all measurement sites, although a few lifestyle factors were found to be significant predictors of SOS at two measurement sites. Unexpectedly, a decreased body mass index (BMI) was found to predict an increased SOS value in the larger bones that were measured ($p < 0.0035$ for the radius and tibia). These results remained significant if the SOS values were adjusted for age. An increased amount of physical activity was also predictive of increased SOS at two sites ($p < 0.05$ for the tibia and phalanx sites). When these SOS values were adjusted for age, the relationship achieved even greater significance ($p < 0.034$). Although low BMI is normally considered a risk factor for osteoporosis, we must consider that intense physical activity could

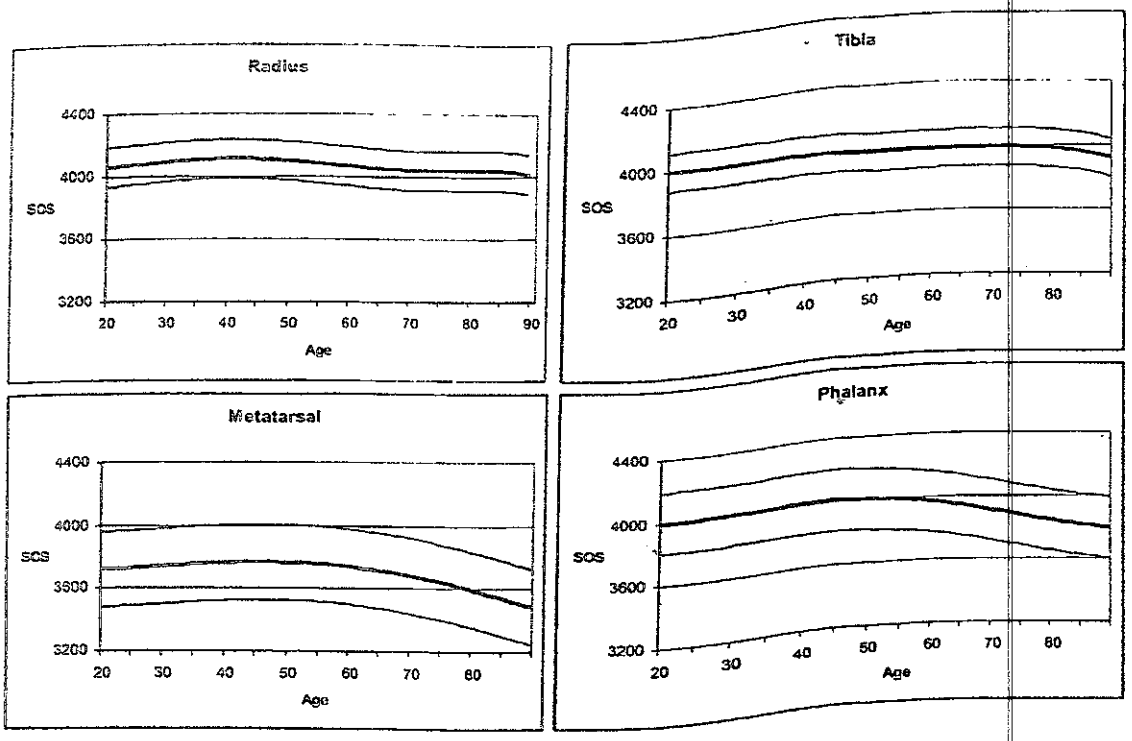

Fig. 1. Moving average SOS in males at four skeletal sites. *Note:* Curves are smoothed with a moving average of ± 5 yr, with reference lines included to show ± 1 standard deviation from the moving average (SD calculated at peak SOS attainment). SOS = speed of sound in meters per second.

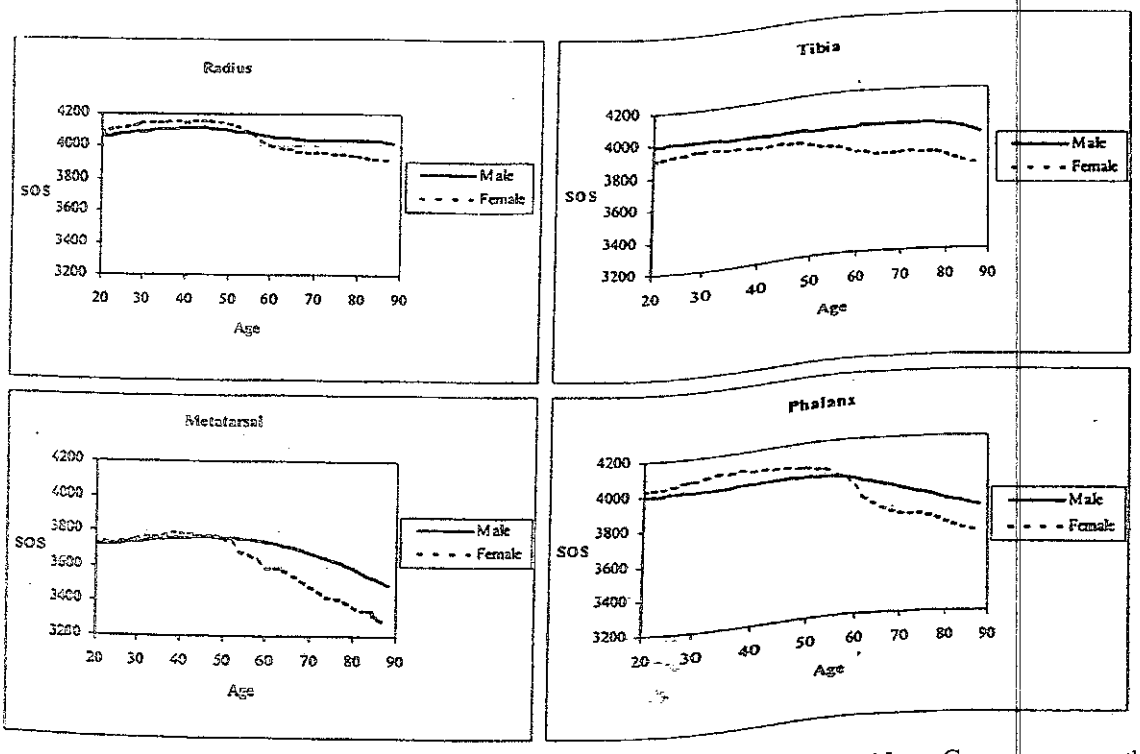

Fig. 2. Comparison of male and female SOS reference curves at four skeletal sites. *Note:* Curves are smoothed with a moving average of ± 5 yr. SOS = speed of sound in meters per second.

lower BMI while increasing bone strength as a result of increased weight-bearing activity. No significant relationship was found between SOS and height, weight, calcium intake, alcohol consumption, tobacco use, family history of osteoporosis, or family history of hip fracture.

Discussion

The last decade has seen the conception and evolution of QUS technologies for use in widespread fracture risk assessment. Currently, bone mineral density (BMD), measured by DXA scanning, is considered to be the most important measurable factor in the assessment of fracture risk *(29)*. Unfortunately, disadvantages of DXA scanning, such as cost, size, and requirement for specialized operators, dictates that this technique is not ideal for screening. This will be especially true in the future, because with our aging population, fractures in North America will increase significantly *(1,3)*. Furthermore, DXA does not reflect structural properties of bone, such as elasticity and porosity, which may contribute independently to fracture risk *(5,8,17,30)*.

Recent research has established that the peak bone mass may be reached at different ages at different skeletal sites *(31–34)*. Lumbar spine BMD measurements in men over the age of 65 may also be altered by skeletal and extraskeletal artifacts *(5,6,24,25)*. Therefore, measurement of BMD using DXA at just the hip and spine might limit the available information when the risk of fracture of any bone as a result of osteoporosis is to be assessed. QUS devices are well suited to deal with these possible problems in skeletal assessment. Peripheral site measurement avoids interference from artifacts in the spine. Measurement at multiple sites provides more information for skeletal assessment, which might reduce the discordance that has been observed when diagnosing osteoporosis using a single skeletal site *(35,36)*.

This study established a reference database for SOS at multiple skeletal sites in Caucasian North American males, using the Sunlight Omnisense. The results clearly demonstrate a decline in SOS with age at the phalanx and metatarsal sites. SOS peaks at both of these sites in the fifth decade and begins to decline at a rate of 1.5–2 m/s/yr early in the sixth decade. The rate of decline continues to increase throughout life at the metatarsal site, reaching about 5–8 m/s/yr in the seven decade, 8–10 m/s/yr in the eighth decade, and 10–12 m/s/yr in the ninth decade. The rate of decline in phalanx SOS increases from 2 m/s/yr at age 50 to 7 m/s/yr at age 70. The rate remains between 5 and 7 m/s/yr for the remainder of life. Similarity between the declines in SOS and BMD reference data is likely reflective of the dependence of SOS on bone density. The different ages at which peak values are attained [usually third or fourth decade for BMD *(37–39)* and fifth decade for SOS in this study] indicate that some component other than density may also play a role in determining SOS. Earlier studies may support this theory by demonstrating the ability of QUS to predict fracture risk, independent of BMD *(7,9,20,40)*. See the review by Njeh and colleagues for discussion of the possible role of structure in QUS measurement *(41)*.

The radial SOS also peaks in the fifth decade. The rate of decline is 3–4 m/s/yr from age 48 to 70, but decreases to near zero as the radial SOS reaches a plateau from age 70 to 84. The SOS resumes its decline again late in the ninth decade. The uneven decline in SOS was unexpected. Most studies that have examined total radial BMD or radial fracture have not detected a disruption in BMD decline or radial fracture patterns later in life. However, two studies that specifically investigated the cortical layer of the radius reported an increase in radial cortical BMD in men over the age of 70 *(42,43)*. Because the "critical angle" technique utilized by the Omnisense primarily reflects the status of cortical bone, the observed plateau in SOS might be indicative of this increase in cortical BMD in the eighth decade. The SOS measurements can also be influenced by factors other than density, including cortical thickness and porosity, but the effect of age on these factors is not well understood.

Tibial SOS did not demonstrate an age-related decline between the ages of 20 and 80. The mean SOS values ranged from 3980 to 4001 m/s for this time period. The fixed nature of tibial SOS was surprising, although it should be noted that tibial shaft fracture does not regularly follow a consistent age-related pattern *(44–46)*. A similar study to collect normative SOS data also found a linear pattern at the tibia. Stegman et al. found mean SOS results of 3898–3989 m/s for men aged 30 and up, with a

decline of only –1.7 m/s/yr *(47)*. Studies have confirmed a correlation between tibial SOS and cortical density, cortical thickness, and cortical elastic modulus *(48,49)*. Isolated experiments have suggested that cortical elastic modulus and tibial BMD do not decline with age *(50,51)*. Although these findings would help to explain the observed tibial SOS, the evidence is unconvincing. Error may also have been introduced by using a convenient sample, as most of the older men were ambulatory and active. Finally, the cortical bone measured by the Omnisense may not reflect any decrease in trabecular BMD.

The meaningfulness of results at each of the four measurement sites is an important concern, especially for clinicians. Because the tibia does not demonstrate a visible peak in SOS or a decline with age before the eighth decade, this site will be useful for identifying men with low T-scores, but the use of *z*-scores would be redundant. The metatarsal site demonstrates a suitable age-related decline in SOS, but measurement difficulties cause loss of precision, resulting in unexpectedly large fluctuations in SOS with age and differences between study centers.

Our study is not without limitations. Convenience sampling introduces an inherent potential for bias. For example, study participants who responded to our advertisement about bone research may be more likely to have stronger bones than the actual population that they are representing. The effects of such a bias are mitigated in normative data collection, because those who are unhealthy (in any way that may affect their results) are excluded from participation.

In summary, this cross-sectional study has shown that the Sunlight Omnisense—a new, inexpensive, portable QUS device—is able to detect changes in the sound propagation properties of cortical bone at multiple sites in a healthy Caucasian male population. Further work is needed to determine how to most effectively utilize the multiple-site capability of this machine to evaluate fracture risk. If multiple-site measurement can improve the accuracy of fracture risk assessment, the efficacy of expensive pharmacotherapies can be monitored and we can then provide more cost-effective osteoporosis treatment. Comparative studies with techniques like peripheral quantitative computed tomography (pQCT) would also be useful to elucidate the structural elements of the bone that determine SOS.

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