Journal of Clinical Densitometry, vol. 4, no. 3, 239–248, Fall 2001

1094-6950/01/4:239–248/$12.50

Original Article

Multisite Bone Ultrasound Measurement on North American Female Reference Population

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Abstract

The Sunlight Omnisense is a portable quantitative ultrasound device that measures speed of sound (SOS) at multiple skeletal sites and therefore has the potential to provide a more complete assessment of an individual's overall fracture risk than single-site measurements such as the calcaneus. To provide a robust normative female database, 545 healthy Caucasian women ages 20–90 were recruited at five centers across North America. SOS measurements were obtained from the distal one-third radius, proximal third phalanx, midshaft tibia, and fifth metatarsal. The results demonstrate that peak SOS occurs around the age of 40, with maximum mean values of 4161, 3928, 3786, and 4092 m/s seen at the radius, tibia, metatarsal, and phalanx, respectively. Maximal rate of decline of SOS was seen in the decade following menopause (–12.4, –9.2, –12.1, and –18.8 m/s at the radius, tibia, metatarsal, and phalanx, respectively). Reproducibility between successive measurements indicates high precision, with standardized coefficients of variance ranging between 1.5 and 4.5%. Greatest precision was seen at the metatarsal. Further work is required to clarify the biologic significance of multisite SOS measurements and their use in the assessment of fracture risk.

Key Words: Bone ultrasound; female reference database.

Introduction

An increasing number of strategies for measuring bone mass have been developed, allowing new insights into skeletal biology *(1)*. An assessment of an individual's global risk of fracture may be based on measurements of bone parameters at any of several sites. Central sites of hip and spine may offer additional advantage in assessing site-specific risk as well as offer the opportunity to assess longitudinal changes in bone mass. Most devices used for estimating bone strength (both dual X-ray absorptiometry [DXA] and ultrasound [US]) at peripheral sites are limited by their ability to measure only one skeletal site. Furthermore, because of discordance among skeletal sites, it is not unusual for patients with normal bone mass at one site to have a low bone mass at another *(2)*. In light of this, it has been proposed that most patients measured with a peripheral device will also require a central measurement *(3)*.

Received 12/13/00; Revised 01/19/01; Accepted 02/01/01.
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A clear understanding of the differences in the attainment of peak bone mass at different skeletal sites, as well as the different patterns of loss, is required for appropriate interpretation of bone measurements at multiple skeletal sites. Although longitudinal measurements are preferable, earlier information may be obtained using cross-sectional data from healthy, free-living volunteers. Later, prospective correlation with fracture incidence may determine the relative fracture risk associated with different levels of bone mass at different sites.

The Sunlight Omnisense™ (Sunlight Medical, Rehovot, Israel) is a noninvasive device that measures US velocity along the length of a bone *(4)*. The technique is applicable to superficial bone sites; is not significantly affected by the thickness of SC tissue *(5)*; and, unlike other quantitative ultrasound (QUS) techniques, permits measurements to be made at multiple peripheral sites. The ability of cortical bone speed of sound (SOS) to predict fracture is likely to be owing to excess bone resorption at cortical, as well as trabecular, sites following menopause. Given that osteoporosis may affect different bones to varying degrees, and that therapeutic decisions frequently rely on sequential observations in a single patient to establish the pattern of bone loss in one or more sites, this portable technique has the potential to facilitate widespread screening for osteoporosis. This, in turn, requires the creation of robust reference databases on which to base patient management decisions.

The purpose of the present study was to create a reference database of SOS values in a North American Caucasian female population. The patterns of attainment of peak bone mass and its subsequent decline in later years will serve as a basis for future investigations aimed at establishing the fracture risk associated with the changing US properties of bone.

Subjects and Methods

Subjects

Women were selected for the study if they had no history of osteoporotic fracture or chronic condition affecting bone metabolism such as hyperparathyroidism, diabetes mellitus, hyperthyroidism, inflammatory arthritis, endogenous or iatrogenic glucocorticoid excess, or malabsorption. No subject had had exposure for more than 1 yr within the preceding 3 yr to a medication affecting bone such as an anticonvulsant, an immunosuppressive, a chemotherapeutic, a gonadotropin-releasing hormone analog, a bisphosphonate, estrogen, a selective estrogen receptor modulator (such as raloxifene or tamoxifen), calcitonin, or fluoride. All patients gave informed, written consent.

Description of Device

The Sunlight Omnisense Ultrasound 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 handheld probe designated for different skeletal sites. The same probe contains two different transducers (signal receivers), 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. Briefly, the transducer generates an array of US 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 are refracted such that their subsequent direction of travel through the bone is along its long axis, within the bone and parallel to its surface. A small fraction of the original beam is detected by the receiver, and the first waves to be detected are used to calculate the SOS. The value generated is compared to a young adult and an age-matched population, to generate T- and Z-scores, respectively. All machines were cross-calibrated by the manufacturer before being shipped to each center.

Measurements

SOS measurements were made in each patient at the distal one-third of the radius (RAD), proximal phalanx of the third finger (PLX), fifth metatarsal (MTR), and midshaft of the tibia (TIB) 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 US gel. For the radius, a point midway between the elbow and the tip of the third digit was used as the centring point for the US beam. For the TIB, with the knee flexed to 90° and the heel on the ground, a point equidistant between the plantar surface of the foot and

the soft tissue above the distal portion of the femur (over the region of the tibial crest) was used. For the MTR, a straight line was drawn from the tip of the lateral malleolus to the head of the MTR, with the ankle rotated medially approx 15°. A second line, drawn medially at 90° to the first, was then used as the positioning point for the proximal aspect of the US probe. For the PLX, a gage was used to measure the length of the medial phalanx of the same finger, with all phalanges flexed to 90°. With the finger still flexed, a point was marked on the proximal phalanx at a distance from its base equal to the measured length of the medial phalanx and used to position the proximal portion of the US probe.

To document the reproducibility of repeated measurements, the SOS was measured three times at each skeletal site in 15 patients (10 premenopausal, 5 postmenopausal), generating a total of 45 pairs of measurements at each site. Six different operators participated in the study.

Subjects were said to have discordant results if they had a T-score of –1 or above at one site in association with a T-score of –2.5 or below at another site.

Statistical Analyses

Normative reference curves of SOS measurement over the age range of 20–90 were generated by the moving average. Each point of age is represented by an average over a window of ±5 yr. The moving average technique was applied to the reference curve build of points for each year, in order to smooth the curve. The annual decline rate between 40 and 80 yr of age is estimated by the slope of the linear regression. The possible association of SOS with variables such as alcohol consumption, body mass index (BMI), physical activity, cigarette smoking, and family history of osteoporosis or hip fracture was tested by analysis of variance with age as a covariate in the model. Correlations of SOS measurements among sites were determined using Pearson's coefficient correlation. The rate of disconcordance in SOS among sites, defined by a T-score of –2.5 at one site and a T-score of –1.0 at another site, was evaluated for each pair of sites (RAD-PLX, RAD-TIB, RAD-MET, TIB-MET, TIB-PLX, and PLX-MET), by calculating an odds ratio (OR), in a logistic regression model. The probability of disconcordance is given by the OR for an interval 10 yr since menopause.

Table 1
Demographic Characteristics of Study Population

	n (%)
Age (yr)	
20–29	107 (19.6)
30–39	115 (21.1)
40–49	102 (18.7)
50–59	86 (15.8)
60–69	67 (12.3)
70–79	46 (8.4)
80–90	22 (4.0)
Total	545 (100.0)
Mean ± SD	47.5 ± 17.3
Range	20–90
Physical activity	
Seldom/never	94 (17.2)
Once per week	89 (16.3)
Several times per week	266 (48.8)
Daily	96 (17.6)
Total	545 (100.0)
BMI (kg/m^2)	
≤25	314 (57.6)
26–30	158 (29.0)
31–35	55 (10.1)
35+	18 (3.3)
Total	545 (100.0)
Mean ± SD	25.0 ± 4.6
Range	17–48
Alcohol consumption	
Never	173 (31.8)
Past	41 (7.5)
Current	330 (60.7)
NR[a]	1
Total	544 (100.0)
Smoking	
Never	380 (69.7)
Past	121 (22.2)
Current	44 (8.1)
Total	545 (100.0)

[a] NR, no response.

Results

In five centers across North America, of 573 healthy Caucasian females who answered advertisements in newspapers, and at educational institutions, community centers, and nursing homes, 545 (mean age of 47.5 ± 17.3 yr, range of 20–90 yr) were eligible for the study. Table 1 presents the demographic details.

Table 2
Mean SOS ± SD by Decade at Four Skeletal Sites

Age	Mean SOS ± SD at radius	Mean SOS ± SD at tibia	Mean SOS ± SD at metatarsal	Mean SOS ± SD at phalanx
20–29	4103 ± 107	3929 ± 143	3735 ± 201	4033 ± 165
30–39	4150 ± 93	3928 ± 144	3777 ± 219	4092 ± 165
40–49	4161 ± 130	3925 ± 119	3786 ± 211	4068 ± 168
50–59	4095 ± 131	3878 ± 150	3670 ± 223	4034 ± 208
60–69	3949 ± 125	3801 ± 134	3588 ± 225	3821 ± 197
70–79	3921 ± 149	3829 ± 153	3408 ± 189	3753 ± 163
80–90	3921 ± 149	3739 ± 159	3353 ± 244	3663 ± 166

SOS Measurements

Mean SOS measurements by decade and according to site are given in Table 2 and reference database curves by site are shown in Fig. 1. The moving average SOS (averaged over an age window of ±5 yr around each age point) increased to a peak at around the age of 40, with an overall plateau between ages 32 and 44. Thereafter, in the phalanx, radius, and tibia an acute decline followed, with a maximum rate of fall of SOS around the age of 58, 8 yr after the mean age of menopause of the study group. Between the ages of 65 and 90, this decline was slower. Linear regression models show that both a straight line and quadratic fit are highly significant ($p < 0.001$) in this region of the graph. In the metatarsal, SOS declines in a more linear fashion from midlife. Table 3 shows the rate of decline of SOS, for each site, between the ages of 40 and 80.

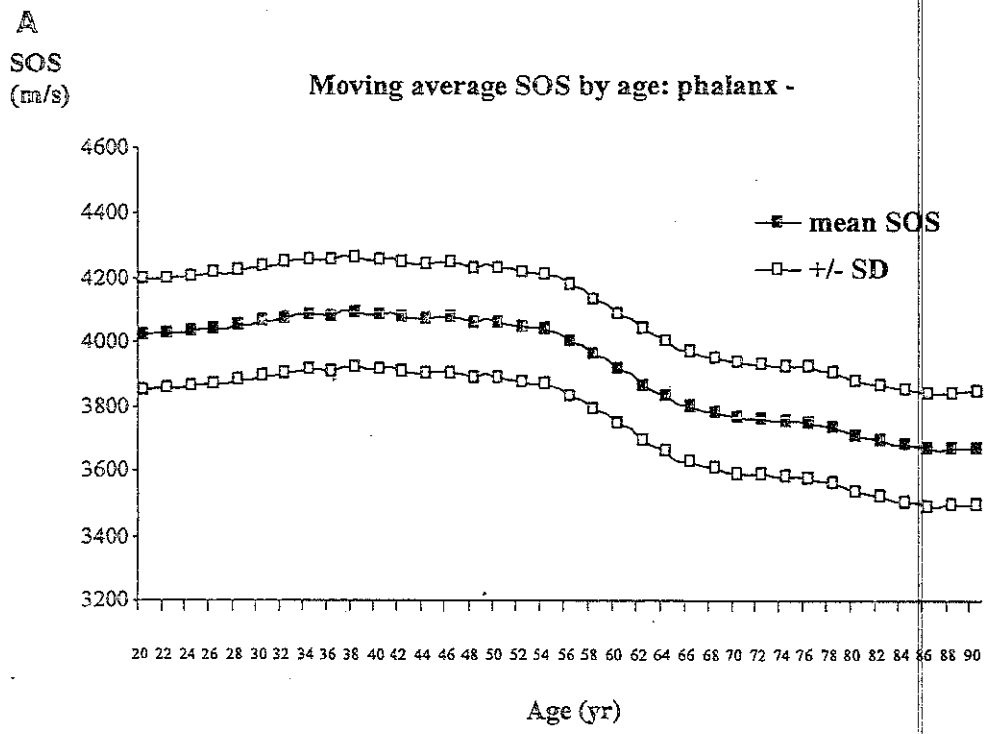
Associations between the age-adjusted mean SOS and smoking (either previous or current), alcohol consumption, physical activity, BMI, family history of osteoporosis, or family history of hip fracture were not statistically significant.

For the precision study, data are presented as the standardized coefficient of variation (SCV), using two models (Table 4). In one, the range of parameters is defined as the 95th–5th centiles of the normative database, according to the model of Miller et al. *(6)*. In the second, the full range of measured parameters (maximum–minimum SOS) in the normative database was used. For each of these methods, the SCV was in the range of 3–4.5 and 1.5–2.7%, respectively (Table 4).

Table 5 presents the correlation coefficient of SOS among sites. Although statistically significant for each combination of sites (radius-tibia, radius-metatarsal, and so on), there were several subjects with a T-score of –2.5 or less at one site and a T-score of –1 or above at another. The numbers of subjects with discordant T-scores between any two skeletal sites is given in Table 6, which is divided into three groups according to menopausal status (premenopausal, 1–15 yr postmenopausal, and >15 yr postmenopausal). The number of subjects with discordant T-scores was significantly less in the premenopausal compared with the two other groups. The logistic regression model, when applied to postmenopausal subjects, revealed that this discordance significantly increased with increasing years since menopause (Table 7). The OR for 10 yr since menopause for radius with other sites was 1.50–1.60, and it was higher for tibia with other sites (OR = 2.12–2.14).

Discussion

At present, bone mineral density (BMD) is the most important measurable factor that is able to predict bone fragility *(7)*, and its measurement therefore represents a vital tool for the identification and possible treatment of those individuals most at risk of fracture. While axial DXA is now the accepted standard tool for assessing osteoporosis, peripheral approaches such as peripheral DXA (pDXA) and QUS have some advantages. These include the relative cost, size and portability of the devices, and lack of ionizing radiation. Further, it is known that the skeleton matures at varying rates, such that peak bone mass may occur at different times in different skeletal sites. Hence, BMD measurements may reveal significant discordance



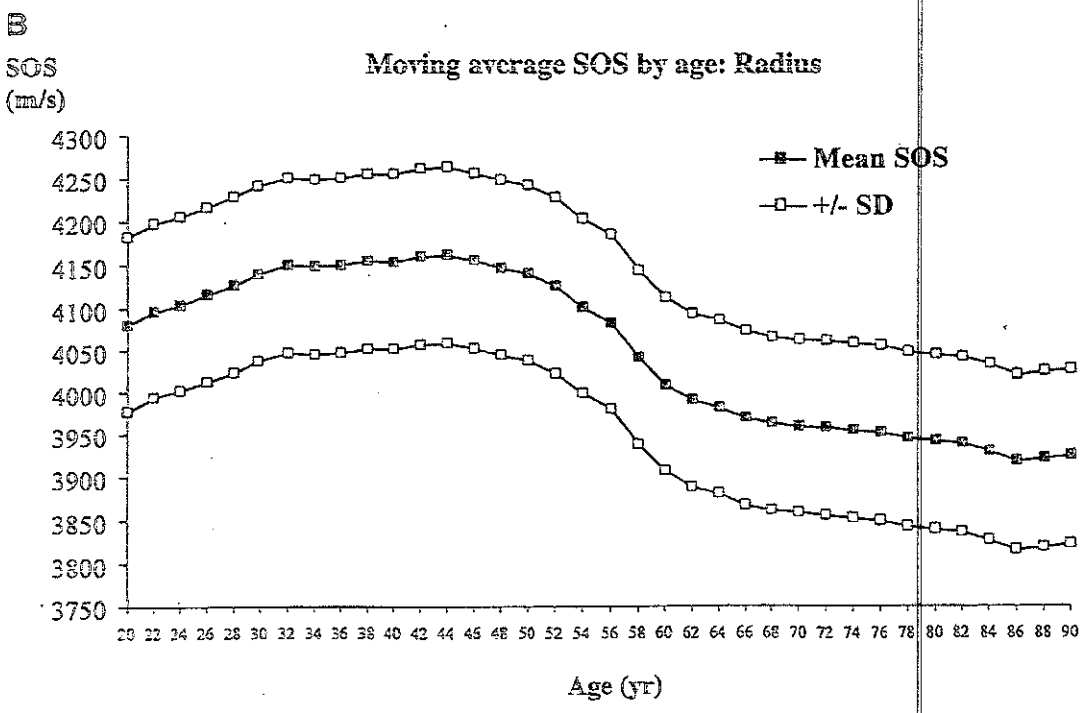
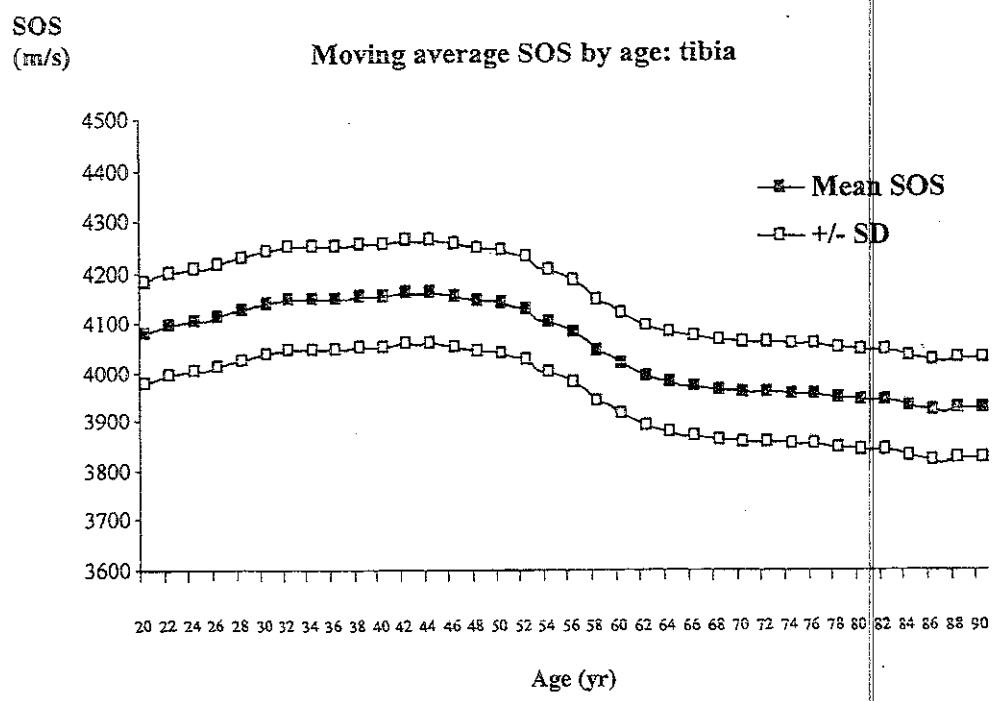


Fig. 1. Normative database curves for SOS in the population. (A) Phalanx; (B) radius; (C) tibia; (D) metatarsal.

C



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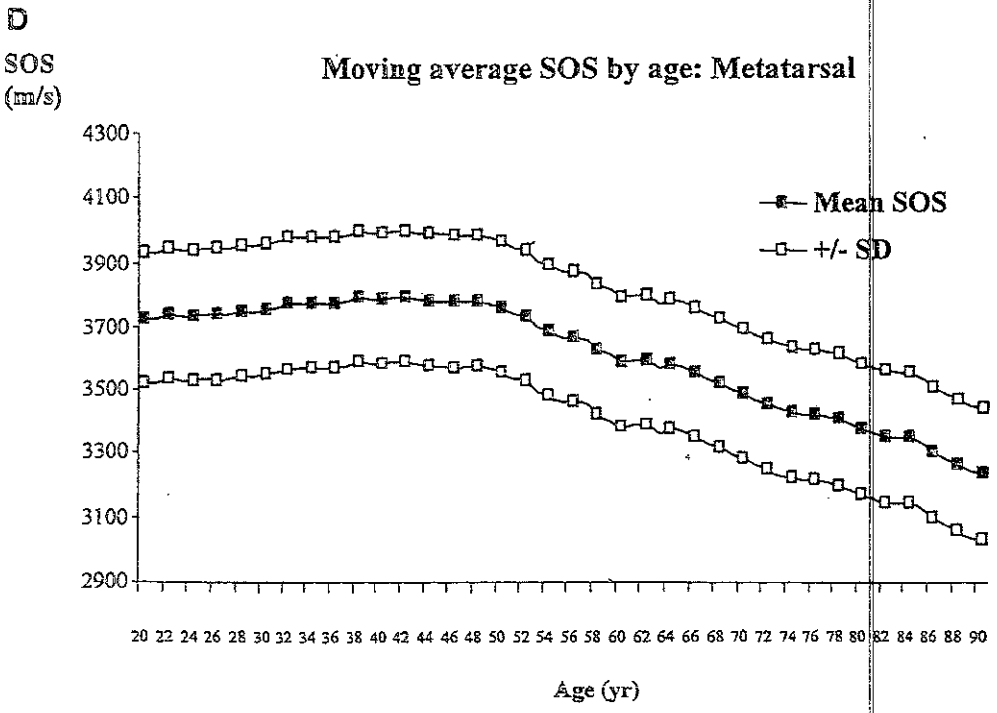

Fig. 1. *Continued*

Table 3
Rate of Decline of T-score at Each Site Between Age 40 and 80[a]

Site	Annual change in ΔT-score (ΔSOS)	SE (ΔT-score)	*p* value	R^2
Age 40–80				
T-RAD	–0.072 (–7.3 m/s)	0.007	<0.001	0.271
T_TIB	–0.026 (–3.9 m/s)	0.005	<0.001	0.091
T_MTR	–0.058 (–11.9 m/s)	0.006	<0.001	0.273
T-PLX	–0.068 (–11.7 m/s)	0.006	<0.001	0.321
Age 50–65				
T-RAD	–0.122 (–12.4 m/s)	0.024	<0.001	0.17
T_TIB	–0.061 (–9.2 m/s)	0.018	0.001	0.08
T_MET	–0.059 (–12.1 m/s)	0.021	0.005	0.06
T-PLX	–0.109 (–18.8 m/s)	0.022	<0.001	0.17

[a] R^2 denotes the relative amount of the total variance that is explained by age.

Table 4
SCVs at Different Skeletal Sites Using Two Different Models

	n	Mean SOS (m/s)	Root MSE[a]	CV (95% CI)[a]	5th centile	95th centile	95th–5th centiles	SCV[a] (%)
Radius	45	4136.3	16.7	0.4 (0.39–0.42)	3820	4295	475	3.5
Tibia	45	3889.4	17.7	0.46 (0.36–0.56)	3613	4119	506	3.5
Metatarsal	45	3625.8	24.1	0.66 (0.52–0.8)	3265	4078	813	3.0
Phalanx	45	3955.9	32.6	0.82 (0.65–0.99)	3616	4335	719	4.5
Radius	45	4136.3	16.7	0.4 (0.39–0.42)	3532	4490	475	1.8
Tibia	45	3889.4	17.7	0.46 (0.36–0.56)	3418	4320	506	2.1
Metatarsal	45	3625.8	24.1	0.66 (0.52–0.8)	2897	4555	813	1.5
Phalanx	45	3955.9	32.6	0.82 (0.65–0.99)	3361	4614	719	2.7

[a] MSE, mean square error; CI, confidence interval; SCV (%), standardized CV as a percentage.

Table 5
Pearson Correlations of SOS Measurements Among All Four Sites[a]

	RAD	TIB	MET	PLX
RAD	1	0.4	0.45	0.5
TIB		1	0.26	0.32
MTR			1	0.5
PLX				1

[a] All correlations are statistically significant with $p < 0.001$.

Table 6
Numbers of Patients with Discordant T-scores Between Any Two Skeletal Sites, According to Menopausal Status

	Premenopausal (n = 344), T-score = –1			
	Rad	Phalanx	Tibia	Metatarsal
Rad	—	5	5	5
Phalanx	0	—	0	1
Tibia	3	4	—	3
Metatarsal	1	1	1	—
	Postmenopausal 1–15 yr (n = 97), T-score = –1			
	Rad	Phalanx	Tibia	Metatarsal
Rad	—	7	11	7
Phalanx	2	—	7	2
Tibia	1	3	—	1
Metatarsal	2	1	3	—
	Postmenopausal > 15 yr (n = 97), T-score = –1			
	Rad	Phalanx	Tibia	Metatarsal
Rad	—	2	9	3
Phalanx	6	—	13	4
Tibia	1	1	—	0
Metatarsal	3	1	9	—

Table 7
OR for Discordance Between Pairs of Sites for 10 yr Since Menopause, Estimated in Logistic Regression Model

Site	β-Coefficient (ΔT-Score)	SE (β) (ΔT-score)	OR[a]	95% CI	p value
RAD-PLX	0.044	0.017	1.55	1.11–2.17	0.009
RAD-TIB	0.047	0.015	1.6	1.19–2.15	0.001
RAD-MET	0.046	0.018	1.58	1.11–2.25	0.011
TIB-MET	0.075	0.019	2.12	1.46–3.07	<0.0001
TIB-PLX	0.076	0.015	2.14	1.59–2.87	<0.0002
MET-PLX	0.068	0.024	1.97	1.23–3.16	0.005

[a] OR for 10 yr since menopause.

among various skeletal regions *(2,3)*. pDXA units are able to measure BMD at sites other than the hip and spine but, like most QUS machines, are single-site devices. Alternative techniques will be required if a more complete assessment of an individual's risk of fracture is to be made available. Given that it is well known that the risk of fracture changes with age, it is important to establish for any new modality of measurement its relationship to age. If, in turn, management decisions are to be made using such techniques, information will be required about the biologic relevance of the measurement being made.

The present study clearly demonstrates that the speed of conduction of US through bone, as deter-

mined by Sunlight Omnisense, shows a decline postmenopausally in women. There are, however, important differences in the patterns of age-related values, suggesting that SOS is not simply a surrogate measure of BMD. BMD characteristically reaches a peak in the middle of the third decade of life *(8,9)*, whereas our study demonstrates a peak SOS around the age of 40, with a plateau between ages 32 and 44. These data are virtually identical to a recently published database from 1521 Israeli women *(10)* and are in keeping with other studies indicating that QUS properties peak later in life *(11)* than measurements of BMD *(12)*. In turn, this would imply that, in addition to the acquisition of bone mass, some biologic property of bone continues to change, and therefore alter SOS, for the next 10–15 yr. Thereafter, SOS declines, most dramatically in the decade following menopause at the phalanx, radius, and tibia and, later, in a more gentle linear fashion in all areas studied. This sharp postmenopausal decline is interesting, given that it is well recognized that estrogen withdrawal is characteristically associated with decreases in BMD that are more marked in trabecular than cortical bone. Given that SOS measurements are dictated by the outermost 3–5 mm of (cortical) bone, this dramatic postmenopausal decline would imply a change in some bone properties that affect SOS propagation, possibly related to cortical porosity and thinning. This factor is likely to be mechanically relevant, given that cross-sectional studies indicate that SOS measured by this technique at multiple sites is better able to discriminate hip fracture than a single-site determination *(13)*. Furthermore, there is evidence that SOS measured at peripheral sites is able to distinguish hip fracture from nonfracture subjects *(14)*. The potential pitfalls of using a measurement at a single site to quantify fracture risk throughout the skeleton are emphasized in the present study by the numbers of patients showing discordance among sites (Table 5). Here, we have chosen to take discordance as a T-score of –2.5 at one site in association with a T-score of –1 at another, to reflect clinical practice in which decisions are frequently made on the basis of BMD measurements in the osteopenic/osteoporotic range. The number of subjects to which this applies increases progressively with time after menopause, suggesting that the changing bone properties are estrogen dependent. However, this is distinct from the characteristic pattern of changes in BMD observed in postmenopausal women, in whom there is frequently considerable discordance between lumbar spine (LS) and femoral neck (FN) sites in the decade after menopause, followed by progressive concordance with each subsequent year *(15)*. Together with the different age at which SOS peaks, this suggests that SOS is dictated by bone properties other than simple BMD. The higher discordance with tibia is expected, given that this site had the lowest annual slope during the decade postmenopause.

The pattern of change in SOS with age reported in our study contrasts with previous studies *(16,17)*, in which peak SOS measured by Lunar Achilles occurred around the age of 30. Such differences are likely owing to the different bone composition present at the different sites used in each study and that Lunar Achilles technology uses through transmission of US, as opposed to the axial transmission utilized in our study.

For a technique to be useful in the serial assessment of bone, precision (the extent to which multiple measurements at the same site deviate) is critical. Although the conventional coefficients of variation (CV) (defined as the ratio of absolute precision to the mean) appear impressive (0.30–0.99%, Table 1), indicating high precision, it is important to recognize that this figure is, in large part, governed by the unit of measurement (in this case SOS). Given that a measurement value of zero has no meaning in the context of SOS (the lower limit of SOS through water being 1500 m/s), a conventional CV also becomes less useful as an indicator of "true" precision. Alternative measures of precision, known as SCVs, have therefore been proposed *(6,18)*. Although the details of the calculation differ slightly between each of these models of precision, a common principle is the replacement of the absolute mean by an alternative value as the range of the measure. Miller et al. *(6)* have proposed the 5th–95th percentile as the range of parameters, whereas Blake and Fogelman *(18)* replace the absolute mean with the population standard deviation. Herein, two calculations of precision are presented: one using the model of Miller et al. *(6)* and another in which the 95th–5th centiles is replaced by 95% of the range of parameters recorded in the entire study. These two models give SCVs that are in the same range as those achieved by most DXA technologies, suggesting that this technique has the potential to provide information on which to base patient management decisions.

The precision error is of the order of the maximum rate of decline of SOS.

In summary, the present cross-sectional study has shown that Sunlight SOS, a new, portable, noninvasive technique, is able to detect changes in the biologic property of bone, in a healthy female Caucasian population ages 20–90, that resemble the changes seen with central skeletal DXA. Although, like BMD, there is a sharp decline in the SOS measurement immediately following menopause, important differences are noted between the characteristics of the decline measured by SOS at different sites and DXA, most notably a later peak. This study further highlights the discrepancies in the biologic properties of bone at different sites, emphasizing the potential for underestimation of skeletal involvement in osteoporosis. It is possible that SOS may provide information about fracture risk assessment additional to simple measures of bone mineral mass. These ultrasound measures may relate to changing structural and mechanical properties of bone. Further work is required in order to elucidate the biologic properties of bone that dictate SOS and to clarify how this translates into an individual's risk of fracture.

Acknowledgment

We are indebted to Diklah Geva for expert statistical assistance.

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