Osteoporos Int (2002) 13:474–479
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Osteoporosis International

Original Article

Multisite Quantitative Ultrasound: Colles' Fracture Discrimination in Postmenopausal Women

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Abstract. Distal forearm fractures are the most common perimenopausal fracture and are generally associated with osteoporosis. The aim of this study was to evaluate the capability of speed of sound (SOS) measurements in cortical bone at the phalanx, radius, tibia and metatarsal to discriminate Colles' fracture cases from controls in postmenopausal women and to compare this with bone mineral density (BMD) measurements obtained by dual-energy X-ray absorptiometry (DXA). Sixty-three postmenpausal Colles' fracture cases and 191 postmenopausal controls had SOS measurements of the radius, tibia, phalanx and metatarsal using a semi-reflection ultrasound technique and BMD measurements of the lumbar spine and proximal femur using DXA. The age-adjusted odds ratios (ORs) for fracture for the SOS measurement sites were 1.50 [95% CI 1.07–2.10] for the radius, 1.23 [0.86-1.76] for the tibia, 1.85 [1.06–3.23] for the phalanx and 1.74 [1.12–2.71] for the metatarsal site. For the BMD measurements the ORs were 1.95 [1.34–2.85] for the lumbar spine, 2.21 [1.43–3.40] for the femoral neck and 2.62 [1.69–4.08] for the total hip. The benefits of combining sites either by taking their average *Z*-score or by using the manufacturer's ORI algorithm were evaluated. The two methods yielded similar results and the ORs for the combination of the radius and phalanx were 2.00 [1.21–3.33], for the radius and metatarsal 1.67 [1.05–2.67], for the phalanx and metatarsal 1.86 [1.11–3.08] and for the radius, phalanx and metatarsal 1.81 [1.07–3.06]. Combinations of DXA sites gave 2.22 [1.44–3.41] for the lumbar spine and femoral neck and 2.41 [1.57–3.70] for the lumbar spine and total hip. In conclusion, semi-reflection ultrasound measurements at the radius, phalanx or metatarsal demonstrated an ability to discriminate fracture cases from controls in postmenopausal Colles' fracture patients, although the odds ratios were lower than with spine and femur BMD.

Keywords: Colles' fracture; Multi-site ultrasound; Postmenopausal women

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Introduction

Distal forearm fractures are the most common perimenopausal fracture and are generally associated with type 1 (postmenopausal) osteoporosis [1–4]. The most frequent distal forearm fracture is the Colles' fracture, which usually results from a fall on an outstretched hand. A Colles' fracture is defined as a fracture of the distal forearm, occurring approximately 2 cm above the lower articular surface of the radius, with dorsal angulation, displacement of the distal fragment of the radius, and with a fracture of the ulnar styloid process [5,6]. Colles' fractures display a different pattern of incidence to spine and hip fractures. Firstly, they occur at an earlier age, with the incidence rate increasing linearly in women between the ages of 40 and 65 years, but thereafter showing no further increase [4,7]. Secondly, there is a seasonal increase in Colles' fractures in the winter, which is associated with the increased risk of falling on days with ice or snow [8]. Low bone mineral density (BMD) is associated with an increased risk of fracture [1,9,10]. In addition, a history of fracture is associated with an increased risk of future fracture at a number of different sites [11].

Dual-energy X-ray absorptiometry (DXA) is currently the most widely used tool in the United Kingdom for the measurement of BMD. However, in many areas there are inadequate resources to meet the demand [12]. Quantitative ultrasound (QUS) offers an inexpensive noninvasive alternative to DXA [12,13] and calcaneal QUS measurements have been shown to be a good predictor of hip fracture in prospective studies [14–16]. QUS devices that perform measurements at other peripheral sites including the phalanges [17,18], tibia [19–21] and patella [22–24] are also available. The majority of QUS devices are limited to single-site measurements. The Omnisense (Sunlight, Rehovot, Israel) was introduced in 1998, and is the first QUS device capable of performing speed of sound (SOS) measurements at multiple skeletal sites. Previous studies using the Omnisense have reported that SOS measurements at the radius, phalanx and metatarsal are able to discriminate fracture cases from controls for hip, vertebral and nonspine fractures [25–28]. In addition, the use of a combination of sites has been demonstrated to improve fracture discrimination [25,28,29].

The aim of this study was to evaluate the Sunlight Omnisense in the discrimination of postmenopausal women with Colles' fractures from postmenopausal controls and to investigate whether the combination of measurement sites improves fracture discrimination.

Materials and Methods

The Omnisense

The Sunlight Omnisense is the first QUS system with the ability to perform SOS measurements at multiple skeletal sites. To accomplish this it uses a number of hand-held probes designed for specific sites. The probes contain an array of transducers, some acting as transmitters and others as receivers. The device uses Fermat's principle [30] to identify the path of the sound wave taking the shortest propagation time between the transmitting and receiving transducers (Fig. 1). The exact path of the signal is determined by Snell's law: as it enters the bone from the soft tissue the signal is refracted through a critical angle which is a function of the ratio of the SOS in soft tissue and bone. After it propagates along the bone, the sound wave emerges at the same critical angle [30]. The time taken for the signal to travel between the transmitting and receiving transducers is used to infer the SOS in bone [28]. The Omnisense is able to eliminate the effect of soft tissue thickness, giving a true SOS measurement of bone [31]. The short-term precision (CV%) for the Omnisense as measured by duplicate scans in 27 subjects was reported to be 0.61% for the radius, 0.43% for the tibia, 0.72% for the phalanx and 0.82% for the metatarsal [27].

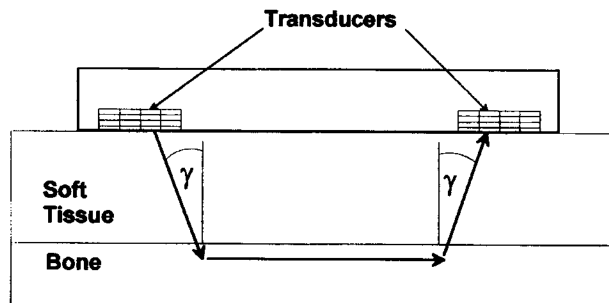

Fig. 1. Cross-sectional diagram of an ultrasound probe used by the Omnisense and the pathway taken by the ultrasound wave.

Subjects

The study population consisted of two groups: (1) healthy postmenopausal women (n = 191) and (2) postmenopausal women with a history of Colles' fracture (n = 63). The exclusion criteria for the healthy postmenopausal women included: a menopause before the age of 45 years; amenorrhea for 6 months or more; a history of drugs or diseases known to affect bone metabolism; or a history of low-trauma fracture [32]. The subjects were recruited from a number of sources: (1) patients referred for DXA screening by their general practitioner (GP); (2) hospital personnel; (3) volunteers from the general population; (4) twin volunteers attending the Twin Research Unit at St Thomas' Hospital (for each monozygotic pair of twins, only one randomly selected twin was included in the study population); (5) Colles' fracture subjects recruited from the above-mentioned areas and in addition from patients attending the Osteoporosis Clinics at Guy's and St Thomas' Hospitals; and (6) volunteers with validated Colles' fractures enrolled in the Chingford 1000 women study [33]. The study was approved by the Guy's and St Thomas' Hospitals research ethics committees and the Forest Healthcare NHS Trust ethics committee.

Subject Measurement

SOS measurements were performed at the nondominant third proximal phalanx, medial aspect of the 1/3 radius (the contralateral radius was measured on the Colles' fracture patients, whilst the nondominant radius was measured on all others), the anteromedial aspect of the midshaft tibia and the lateral aspect of the fifth metatarsal using the Sunlight Omnisense. The Omnisense device uses a total of three different probes for measurements of the four sites. One probe measures both the radius and tibia, whilst individual probes are used to measure the phalanx and metatarsal. The number of subjects with measurements at all four sites was less than those with radial and tibial measurements due to different probes becoming available at different times. Two Sunlight Omnisense devices were used to collect the data, one based in the Osteoporosis Screening and Research Unit at Guy's Hospital and one based in the Twin Research Unit at St Thomas' Hospital. In addition to SOS measurements all subjects had DXA of the

lumbar spine and proximal femur using a total of four Hologic QDR densitometers (Hologic, Bedford, MA). The two Omnisense devices and four QDR densitometers were cross-calibrated using in vitro and in vivo cross-calibration and any significant differences adjusted for [27].

Statistical Analysis

The mean and standard deviations of SOS and BMD measurements and patient characteristics data were calculated for the postmenopausal control group and fracture group. Z-scores were calculated using the healthy postmenopausal controls and the following formula:

$$Z - \text{score} = \frac{\text{measured SOS} - \text{mean population SOS}}{\text{Population SD}}$$

Logistic regression analysis was used to calculate the odds ratios (ORs) for fracture based on a 1 SD decrease in Z-score. Initially, age, height and weight were adjusted for. However, only age was significant and therefore weight and height were dropped from the equation. The effects of combining sites were examined by averaging the Z-scores for the combination of two or more ultrasound sites. The new Z-scores were divided by the standard deviation of the control group combined Z-scores to adjust the Z-score standard deviation back to 1, therefore still resulting in an OR for a 1 SD decrease [34]. In addition, a second method based upon the manufacturer's ORI and the α values displayed in the algorithm Table 1 were used to combine the sites:

$$\text{ORI (site1, site2)} = \alpha_1 Z(\text{Site 1}) + \alpha_2 Z(\text{Site 2})$$

Because this algorithm resulted in a SD <1, the combined Z-score was once again divided by the SD of the control population Z-score to adjust this SD back to 1. The age-adjusted OR were calculated using logistic regression as for the single-site calculations. Receiver operating characteristic (ROC) curves were also used to calculate the area under the curve (AUC) to evaluate fracture discrimination for both single sites and the combination of sites.

Table 1. ORI algorithm weighting factors for combining sites

Site 1 Site 2	RAD TIB	RAD MTR	RAD PLX	PLX TIB	PLX MTR	MTR TIB
α1	0.541	0.669	0.559	0.481	0.584	0.422
α2	0.467	0.402	0.456	0.522	0.442	0.627

Results

The subject characteristics are shown in Table 2. The fracture cases were significantly older, shorter and lighter than the controls, although their overall body mass index was not significantly different from the controls. The fracture group also had a significantly earlier menopause, being on average 22.9 years after menopause compared with 9.3 years for the controls. All the mean SOS measurements and BMD measurements were significantly lower in the fracture group compared with the control group, although this is in part is due to the age difference between the two groups.

The Colles' fracture patients consisted of 63 patients who had a history of low-trauma Colles' fracture. None of the patients had ever received antiresorptive therapies for osteoporosis, although 9 had received, or were currently receiving, calcium supplements. Twenty-five of the 63 patients had only suffered a Colles' fracture, while the remaining 38 had also suffered fractures at sites in addition to the radius. These included ankle ($n=9$), vertebrae ($n=8$), ribs ($n=5$), shoulder ($n=5$),

Table 2. Subject characteristics

Mean (SD)	Controls	Colles' fracture cases	Colles' fracture cases with other fractures excluded
n	191	63	25
Age (years)	59.02 (7.30)	69.27 (7.50)**	67.56 (6.48)**
BMI (kg/m^2)	25.40 (3.77)	25.31 (3.76)	25.92 (2.94)
Weight (kg)	66.78 (12.02)	63.53 (11.39)*	66.20 (8.28)
Height (m)	161.26 (9.65)	158.04 (7.50)*	159.78 (4.11)
Menopause age (years)	50.39 (9.65)	46.41 (6.23)**	47.48 (4.82)**
YSM (years)	9.31 (7.10)	22.87 (9.86)**	20.08 (69.95)**
SOS (m/s)			
Radius	4053 (118)	3942 (147)**	3964 (113)*
Tibia	3822 (142)	3763 (146)*	3773 (135)
Phalanx	3858 (196)	3674 (168)**	3663 (138)**
Metatarsal	3580 (190)	3381 (245)**	3398 (253)*
BMD (g/cm^2)			
Lumbar spine	0.933 (0.142)	0.794 (0.156)**	0.818 (0.113)**
Femoral neck	0.760 (0.115)	0.635 (0.106)**	0.672 (0.072)**
Total hip	0.896 (0.121)	0.735 (0.137)**	0.795 (0.107)**

BMI, body mass index; YSM, years since menopause; SOS, speed of sound; BMD, bone mineral density.
*$p<0.05$, **$p<0.001$ when compared with the control population.

Table 3. Odds ratios for Colles' fracture cases, including those with additional fractures at other sites

Site	*n* controls	*n* cases	OR	*p* value	95% CI	AUC
Radius	182	57	1.50	0.019	1.07–2.10	0.61
Tibia	189	59	1.23	0.252	0.86–1.76	0.54
Phalanx	128	49	1.85	0.032	1.06–3.23	0.64
Metatarsal	116	35	1.74	0.014	1.12–2.71	0.64
Lumbar spine	188	63	1.95	0.001	1.34–2.85	0.66
Femoral neck	188	63	2.21	<0.001	1.43–3.40	0.68
Total hip	188	63	2.62	<0.001	1.69–4.08	0.74

OR, odds ratio; AUC, area under the curve.

Table 4. Odds ratios from combining sites

Site	*n* controls	*n* cases	OR	*p* value	95% CI	AUC
Radius and phalanx	125	44	2.00	0.007	1.21–3.33	0.67
Radius and metatarsal	113	32	1.67	0.032	1.05–2.67	0.64
Phalanx and metatarsal	113	34	1.86	0.018	1.11–3.08	0.66
Radius, phalanx and metatarsal	110	31	1.81	0.026	1.07–3.06	0.66
Lumber spine and femoral neck	186	61	2.22	<0.001	1.44–3.41	0.69
Lumbar spine and total hip	186	61	2.41	<0.001	1.57–3.70	0.71

humerus ($n=5$), toes ($n=3$), elbow ($n=2$), phalanges ($n=2$), patella ($n=2$), metatarsals ($n=2$), femur ($n=2$), hip ($n=1$), tibia and fibula ($n=1$) and scaphoid ($n=1$).

Table 3 shows the results for the Colles' fracture cases including those patients who also sustained other fractures. The ORs per 1 SD decrease in SOS for the ultrasound measurements in this group were 1.50, 1.85 and 1.74, and the corresponding AUC values were 0.61, 0.64 and 0.64 for the radius, phalanx and metatarsal respectively, all of which reached statistical significance. The tibia failed to discriminate fracture cases from controls with an OR of 1.23 (AUC 0.54) which did not reach statistical significance. The OR for the DXA measurements ranged from 1.95 to 2.62 (AUC 0.66–0.74), all of which were highly statistically significant.

The ORs were also calculated for a subset ($n=25$) of patients who had sustained only a Colles' fracture. The ORs in these patients were 1.49 [95% CI 0.90–2.49] for the radius ($n=22$), 1.19 [0.74–1.93] for the tibia ($n=25$), 2.88 [1.27–6.54] for the phalanx ($n=21$) and 1.66 [0.92–2.99] for the metatarsal ($n=15$). The DXA ORs were 2.07 [1.20–3.58] for the lumbar spine ($n=25$), 1.75 [0.98–3.12] for the femoral neck ($n=25$) and 1.79 [1.04–3.07] for the total hip ($n=25$).

Table 4 shows the results obtained by combining sites using the mean *Z*-scores for the total Colles' fracture group of 63 patients. The OR for the radius and phalanx combination was 2.00 (AUC 0.67), demonstrating an improvement in the discrimination of fractures when compared with the single sites alone. The OR for the combination of the radius and metatarsal was 1.67 (AUC 0.64), and the combination of the phalanx and metatarsal resulted in an OR of 1.86 (AUC 0.66) demonstrating no benefit from combining sites in this instance. The combination of the lumbar spine and femoral neck resulted in a limited improvement in fracture discrimination compared with the individual sites alone, whilst no improvement was found when combining the lumbar spine and total hip. When the SOS measurement sites were combined using the ORI algorithm the resulting OR were similar to those obtained using the mean Z-score method, with the radius and phalanx combination yielding an OR of 1.95 [1.11–2.92], the radius and metatarsal 1.61 [1.01–2.58] and the phalanx and metatarsal 1.87 [1.11–3.18].

Discussion

This study evaluated the ability of semi-reflection SOS measurements at the radius, tibia, phalanx and metatarsal, and DXA of the lumbar spine and proximal femur, to discriminate Colles' fracture patients from controls. The OR were 1.50 for the radius, 1.85 for the phalanx and 1.74 for the metatarsal. Omitting patients with fractures at other skeletal sites resulted in similar OR at the radius, tibia and metatarsal, although these failed to reach statistical significance, possibly due to the small numbers in this group. The OR at the phalanx for this group was 2.88, which is significantly greater than for the equivalent OR in the whole group. However, due to the small number of subjects this estimate has a wide confidence interval. The results were lower than reported in recent smaller studies using the Omnisense that included fractures at other skeletal sites [35,36]. Barkmann et al. [29] found age-adjusted ORs in 28 hip, spine, forearm and ankle fracture cases, with 35 postmenopausal controls of 4.5 [1.6–13.0] for the radius and 4.1 [1.5–11.7] for the phalanx, whilst Hans et al. [25] found ORs of 2.4 [1.4–4.2] for the radius and 2.0

[1.4–2.9] for the phalanx using 79 hip fracture patients and 295 controls. Weiss et al. found an OR of 1.92 [1.22–3.02] in their study using 50 hip fracture patients and 130 controls [26]. These studies have predominantly covered hip fracture cases, but provide a general idea of the OR found using semi-reflection ultrasound at peripheral sites. The tibia was unable to discriminate between fracture cases and controls, which is consistent with previous studies [27,36,37]. The BMD OR were significant for all sites and were 1.89 for the lumbar spine, 2.27 for the femoral neck and 2.63 for the total hip. The SOS OR are lower than those found for DXA, which has frequently been found for peripheral measurements in comparison with axial measurements [10].

Previous studies that have investigated the combination of sites found a benefit of using a combination of sites compared with using single-site measurements alone [25,28,37]. When the influence of combining sites to improve fracture discrimination was investigated in this study a slight improvement was found for the use of a combination of sites compared with a single site alone. The best combination of sites was the radius and phalanx, with the OR becoming 2.00 and the AUC improving by 0.03. These results are consistent with previous studies where benefits of a similar magnitude have been observed when combining SOS measurement sites [25,28]. No significant differences were found between the two different methods investigated for combining SOS sites. The combinations of the spine and femoral neck BMD regions of interest also resulted in improved fracture discrimination, whilst no improvement was found for the combination of the spine and total hip.

There are a number of limitations that require discussion. Firstly, this is a cross-sectional study. The control population may not be representative of the general population as a result of the exclusion criteria applied to the recruitment of controls. The majority of SOS ORs were slightly lower than those found for BMD. This may have slightly overestimated the DXA ORs but not altered our conclusions to any degree. In addition, there was a 10-year age difference between the fracture cases and controls. However, all OR results were adjusted for age.

In conclusion, this study has demonstrated an ability of quantitative ultrasound measurements in cortical bone at the radius, phalanx and metatarsal to discriminate between Colles' fracture cases and controls in postmenopausal women, with the sites offering the best fracture discrimination being the phalanx and metatarsal. However, the fracture discrimination capabilities of these measurements do not appear to be as good as those for DXA measurements in the same population. Ideally, further work is required to confirm the fracture discrimination in a prospective study.

Acknowledgements. The authors would like to thank Lisa Carter (research nurse); Fiona Crane, Anita Jefferies and Christine O'Gara, (DXA radiographers); Ursula Perks, Edel Strong, Lucy Campbell, Naomi Welsh, Lucy Wormald, Jane Urwin, Jane Williams, Tracy Harris and Janine Kelleher (Twin Research nurses); Maxine Daniels and Debbie Hart, the volunteers, patients, twins, the staff and patients at the Chingford Osteoporosis Unit and, finally, the National Osteoporosis Society, UK for funding the study.

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Received for publication 6 July 2001
Accepted in revised form 11 December 2001