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Original Article

Discrimination of Proximal Hip Fracture by Quantitative Ultrasound Measurement at the Radius

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Abstract. Osteoporosis is a disease that culminates in fragility fractures and, therefore, imposes major burden on the health economy. In dealing with this worldwide condition, it is prudent to use a reliable, inexpensive, portable diagnostic means that does not use ionizing radiation and is capable of measuring bone properties at several sites. Recently, a quantitative ultrasound device (Omnisense) that measures speed of sound (SOS) at multiple skeletal sites was introduced. The Omnisense combines the 'axial transmission' mode and the critical angle concept. Preliminary reports suggested that of the different skeletal sites measured by this device, the distal third of the radius is the preferred measurement site for osteoporosis. In this cross-sectional study, SOS was determined at the radius using Omnisense in 50 hip-fractured elderly women (group F, age 76.1 ± 6.0 years), 130 elderly controls (group NF, age 71.5 ± 5.2 years) and 185 young healthy controls (group YH, age 40.6 ± 3.0 years). Actual SOS was significantly lower in group F compared with group NF ($p = 0.0001$). Whereas SOS *T*-scores calculated for each woman and stratified into age subgroups within each of the study groups indicate decline from –2.22 to –3.56 in group F and from –1.56 to –3.17 in group NF, there was an increase from –0.02 to 0.03 in group YH. Age- and BMI-adjusted logistic regression for hip fracture discrimination indicated an area under the receiver operating characteristic curve for hip fracture of 0.79 (95% CI, 0.73–0.86; $p = 0.005$) and an odds ratio of 1.92 (95% CI, 1.22–3.02; $p = 0.005$). We conclude that SOS measured at the radius by Omnisense discriminates subjects with hip fracture from controls. Prospective studies are needed to support the role of Omnisense in assessing the risk of hip fracture.

Keywords: Axial transmission; Cross-sectional study; Hip fracture; Osteoporosis; Quantitative ultrasound; Speed of sound

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Introduction

Osteoporosis is a significant cause of morbidity and mortality among postmenopausal women and has major impact on the health economy worldwide [1]. Until recently, the diagnosis of osteoporosis has been based on assessment of bone mineral density (BMD) by means of X-ray energy [2], usually in the form of dual-energy X-ray absorptiometry (DXA) – rendering this technology inaccessible to many patients. Therefore, developing an inexpensive, office-based or portable diagnostic unit that does not use ionizing radiation is highly desirable. The use of transmission quantitative ultrasound (QUS) of peripheral sites for this application has lately gained popularity and has recently been evaluated [3] and reviewed [4]. It is possible that QUS may provide additional information on bone property that is independent of BMD. However, QUS is usually limited to single measurement site, and as the skeleton is not uniformly involved in osteoporosis [5],single-site measurement is of concern.

The recently introduced Sunlight Omnisense (Omnisense) is an ultrasound device capable of measuring bone speed of sound (SOS) at various sites. A previous study [6], performed using an early prototype of the Omnisense, suggests that the prototype device discriminates between subjects with or without fragility fractures by SOS measurements at multiple skeletal sites, and that the distal radius may be the most informative one. In contrast to commonly used calcaneal QUS devices that evaluate ultrasound properties perpendicular to the load vector, determination of SOS by Omnisense along the radius seems more relevant to the mechanical load that is applied along the arm. As hip fracture is the most serious complication of osteoporosis, this cross-sectional study is the first to evaluate the ability of the marketed Omnisense to discriminate subjects who sustained a hip fracture from controls, by measuring SOS at the distal radius.

Subjects and Methods

Subjects

Three groups of women were included in the study:

Group F: patients hospitalized at either the E. Wolfson Medical Center, Holon or 'Assaf Harofeh' Medical Center, Zerifin, Israel for a recent hip fracture. A few additional patients recovering from recent hip fractures in rehabilitation centers were also included in this group. The mean 'age of fracture' was 1.02 years (range 0–9 years).
Group NF: community-residing, age-matched elderly women with no history of hip fracture.
Group YH: young, healthy volunteers from neighboring communities and academic institutions.

Reasons for exclusion from the study were: body mass index (BMI) higher than 35 kg/m^2, menopause before the age of 45 years, history of a non-basal-cell cancer, immobilization for more than months within the preceding year, deformity at the radius, or treatment with bone-affecting medications (glucocorticoid, estrogen, bisphosphonate, calcitonin, fluoride, anticonvulsant or thyroxine without regular medical supervision) for more than a year within the preceding 3 years. Participants were interviewed for confounding variables that affect BMD such as degree of physical activity, consumption of dairy products, alcohol and tobacco.

SOS Measurement

SOS was determined using the Omnisense (Sunlight Ultrasound Technologies, Rehovot, Israel). The Omnisense is designed to measure SOS of ultrasonic waves axially transmitted along bones. For every measurement site a special probe is dedicated. The first probe that was developed and commercialized, and is reported here, is the distal radius probe. The Omnisense successively generates pulsed acoustic waves at a center frequency of 1.25 MHz by means of two transducers located within the ultrasound probe. The ultrasound waves are conducted along the bone and then detected by two different transducers assembled within the probe. By measuring the propagation times along the different trajectories, originating at one of the transmitting transducers and arriving at one of the receiving transducers, the SOS of the bone is determined. The Omnisense detects the first signal that reaches the receiving transducer. According to Snell's Law and the principle of Minimal Action, the first signal arriving always follows a path characterized by entering the bone at the Critical Angle. This angle is defined by the ratio of SOS in soft tissue and bone. The sound wave then propagates inside and parallel to the bone surface, scatters and exits the bone toward the receiving transducer at the same critical angle [6]. The propagation time is related to the bone and soft-tissue SOS, average distance between the transducers and bone, and the inclination angle between the bone surface and the line connecting the two acting transducers. Bone SOS, soft tissue thickness and the inclination angle are determined by a set of three simultaneous equations, each arises from a different propagation path.

During the SOS measurement process, the operator tangentially scans the nondominant limb with the probe using an acoustic coupling gel. While scanning, SOS values are recorded and the bone SOS profile is determined. It takes approximately 20s to obtain a preset number of SOS values that is defined as a measurement cycle. Three measurement cycles are performed and checked for consistency as follows: The 95th percentile, average and the 25th percentile SOS values are computed for each of the three measurement cycles. Their coefficients of variation, CV(P951,P952,P953), CV(Av1,Av2,Av3) and CV(P251,P252,P253), are then determined. If all three coefficients of variation are below 1.2%, the three cycles are declared statistically consistent. If this is not the case, a fourth measurement cycle is performed and the system looks for three out of four consistent measurement cycles using the same algorithm. Only in rare cases, is a fifth measurement cycle required. Once three measurement cycles are statistically consistent, the Omnisense computes the average of the three 95th percentile SOS values. This average is reported as the SOS for the measurement result. Finally, the *T*-score and *Z*-score are provided by comparing the SOS result with the manufacturer's normative database of Caucasian women. For simplicity only *T*-score data will be presented and discussed in this study.

Data Collection and Verification

All data related to the study were recorded on case report forms that were completed at the time of the subjects' evaluation. When available, data were also retrieved from the participants' medical records. Fractures were always verified with the medical-center source documents.

Ethics Consideration

Every participant signed an informed consent. Both local and governmental ethics committees approved this study.

Statistical Evaluation

All data were evaluated by SAS system using the SAS/FSP module with predefined screens enabling smart data entry. On-line data verification included min-max as well as dynamic protection of data entry fields. Mean ± SD of demographic and confounding variables were calculated. The differences between the three study groups were tested by ANOVA and chi-square test. A p value lower than 0.05 was considered significant throughout the study. The possible association of cofactors (age, BMI, consumption of dairy products, tobacco use and alcohol intake) were evaluated in a stepwise logistic regression and a subset of cofactors was defined. This subset was added to a logistic regression model with SOS (Full Model) that estimated the adjusted odds ratio (OR) of a1 SD decrement in SOS for hip fracture. This OR was compared with the OR obtained by a model that examined SOS alone (Reduced Model). In addition, the receiver operating characteristic (ROC) curves of both models were plotted and compared. The area under the ROC curve (AUC) for SOS discrimination of hip fracture is presented with the 95% CI.

Results

Subject Characteristics

Of 104 patients with hip fracture who were approached, 50 were included (group F) and the rest were found noneligible. In group NF (elderly women without hip fracture), 247 women were enrolled and 117 subjects were excluded. Of 218 young healthy volunteers considered for the study, 185 were included (group YH) and 33 were rejected. The proportion of eligible subjects was similar in the three groups. In the entire cohort of women the most common reasons for ineligibility were unacceptable candidate age,disease at both radii, premature menopause, history of a metabolic bone disease and exposure to bone-affecting medications (87, 53, 34, 20 and 16 subjects, respectively). Whereas unacceptable candidate age was the most common reason for candidate rejection in groups F and NF (27 and 60 women, respectively), the most frequent reason in group YH was inaccessibility of SOS measurement site. All participants were Caucasian Israelis and their characteristics are shown in Table 1. Naturally, members of group YH were the youngest. Women of group F were older than the elderly controls. While height was similar in all three groups, both weight and BMI of group NF were higher than that of group F. Therefore, adjustment for age and BMI was included in further analysis.

Dietary Calcium, Smoking and Physical Activity

The overall dietary calcium intake was small in all study groups and is expressed in Table 2 as the amount of liquid dairy products consumed per week. Alcohol consumption was negligible; more than 95% of the participants were only social alcohol users. Therefore, alcohol intake was omitted from further analysis. In contrast to alcohol drinking, 25% of group YH were current smokers, but only about 8% of the elderly women from groups F and NF were active smokers (Table 2). The reported levels of physical activity by the various cohorts of women are also shown in Table 2. As a rule, the daily physical activity was low in all study groups. It was the lowest in group F ($p < 0.05$), and similar in the two nonfractured groups.

Gynecologic History

Members of both groups F and NF had the same 30% rate of surgery-induced menopause while the rest had a natural menopause. Both groups F and NF were menopausal for a comparable period of time (26.4 and 20.9 years, respectively).

SOS Data

Considering entire groups, SOS was significantly ($p = 0.0001$) lower in group F compared with group NF (Fig. 1). However, on subdividing the participants into 5-year age groups, only in the 76–79 year group was the difference in SOS statistically significant ($p = 0.003$).

Table 1. Subject characteristics

	Group F (n = 50)			Group NF (n = 130)			Group YH (n = 185)		
	Mean ± SD	Min	Max	Mean ± SD	Min	Max	Mean ± SD	Min	Max
Age (years)	76.1 ± 6.0[a]	65	85	71.5 ± 5.2[a]	65	85	40.6 ± 3.0[a]	35	45
Weight (kg)	59.4 ± 9.9[a]	40	80	65.9 ± 9.2[b]	45	90	64.1 ± 11.0[c]	39	100
Height (m)	1.59 ± 0.06	1.45	1.75	1.59 ± 0.06	1.47	1.75	1.63 ± 0.06[a]	1.48	1.76
BMI (kg/m^2)	23.5 ± 3.6[a]	16	31	26.2 ± 3.1[a]	18	35	24.0 ± 3.8[a]	16	36

Group F, women with hip fracture; group NF, elderly women without hip fracture; group YH, young healthy females; BMI, body mass index.
[a]p <0.0001 compared with the other two groups; [b]p <0.0001 compared with group F; [c]p <0.005 compared with group F.

Table 2. Risk factors for osteoporosis in the various study groups

Variable	Group F		Group NF		Group YH	
	n	%	*n*	%	*n*	%
Liquid dietary dairy products						
None	3	6.0	2	1.5[a]	3	1.6[a]
<1000 ml/week	31	62.0	44	33.8	66	35.7
>1000 ml/week	16	32.0	84	64.6	116	62.7
Cigarette smoking						
Never	42	84.0	104	80.0	127	68.6
Past smoker	4	8.0	17	13.1	10	5.4
Current smoker	4	8.0	9	6.9	48	25.4
Physical activity						
Seldom	40	80.0	30	23.1	28	15.1
Once a week	5	10.0	31	23.8	58	31.4
Several times a week	3	6.0	53	40.8	67	36.2
Daily	2	4.0	16	12.8[a]	32	17.3[a]

Group F, women with hip fracture; group NF, elderly women without hip fracture; group YH, young healthy females.
p <0.001 as compared with group F.

SOS *T*-scores that were categorized according to age and study groups indicate a decline from –2.22 to –3.56 in group F, and from –1.56 to –3.17 in group NF. However, the *T*-score stayed about the same (between –0.02 and 0.03) in group YH (data not shown).

Logistic regression for identification of cofactors for hip fracture discrimination (Table 3) indicate that age, BMI and physical activity enter this model. However, as the level of physical activity was determined by a recall history, lack of or reduced physical activity frequently results from hip fracture, rather than being a risk factor for the fracture. Therefore, the level of physical activity was not included in the full model. Analysis of hip fracture discrimination by SOS, using the full model (Fig. 2), suggests an OR of 1.92 (95% CI, 1.22–3.02), while the reduced model indicates an OR of 2.16 (95% CI, 1.46–3.19). The ROC curves (Fig. 3) indicate an AUC of 0.79 (95% CI, 0.73–0.86) for the full model and 0.69 (95% CI, 0.61–0.77) for the reduced model.

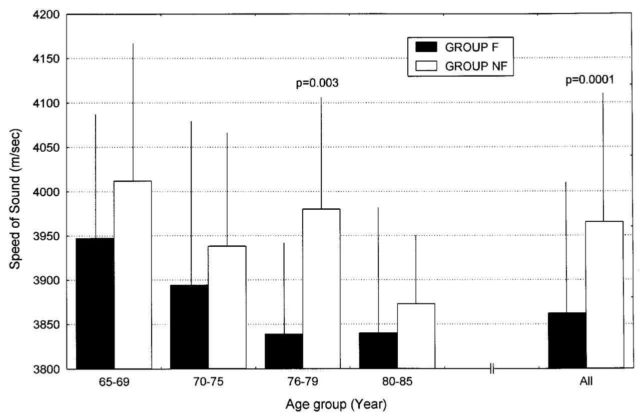

Fig. 1. Age-specific speed of sound measured by the Omnisense at the radius in elderly women who sustained (group F) or did not sustain (group NF) a hip fracture. The vertical lines indicate SD. The *p* values are indicated only when there is significant difference.

Table 3. Identification of cofactors for discrimination of hip fracture by logistic regression

Variable	Parameter ± SD	*p* value
Stepwise model[a]		
Intercept	0.4 ± 3.2	0.9079
Age (Low)	–0.10 ± 0.04	0.0090
BMI (High)	0.26 ± 0.07	0.0003
Physical activity (seldom)	2.54 ± 0.46	0.0001
Full model[b]		
Intercept	–14.8 ± 7.5	0.0491
Age (Low)	–0.09 ± 0.04	0.0092
BMI (High)	0.24 ± 0.06	0.0002
Radius SOS	0.0043 ± 0.0015	0.0052
Reduced model		
Intercept	–18.8 ± 5.1	0.0002
Radius SOS	0.0051 ± 0.0013	0.001

[a]Variables examined: age, BMI, intake of dairy products and tobacco use.
[b]Physical activity was not included in the full model as it was frequently affected by rather than associated with hip fracture.

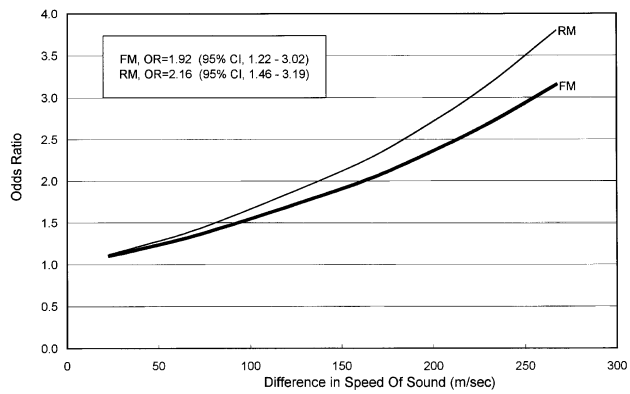

Fig. 2. Odds ratios for discrimination of hip fracture by speed of sound using the full and reduced models (FM and RM, respectively).

Classification of SOS T-scores of both groups of elderly subjects according to WHO criteria concerning BMD is shown in Fig. 4.

The frequency distribution histogram (Fig. 5) indicates a higher proportion of patients reporting hip fracture as SOS decreases. However, groups F and NF overlap at SOS of 3800–3900 m/s.

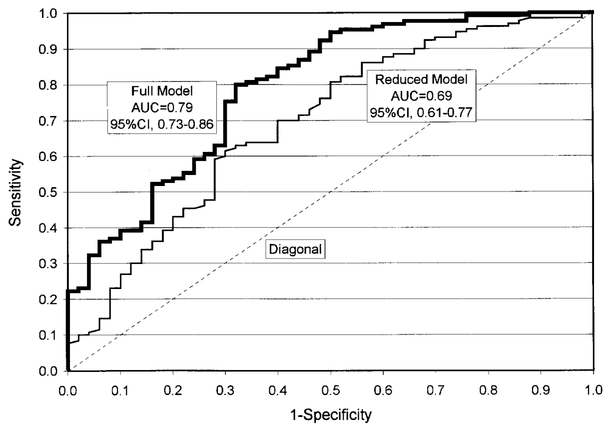

Fig. 3. Receiver operating characteristic curves for discrimination of hip fracture by speed of sound. AUC, area under the curve.

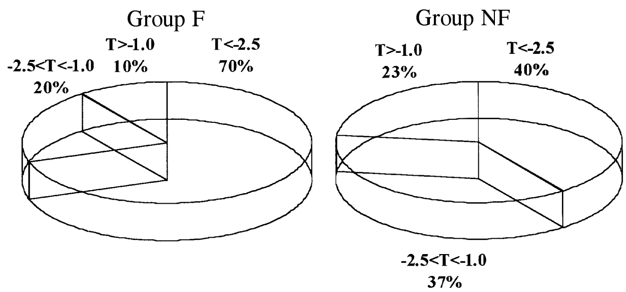

Fig. 4. Classification of in elderly women who sustained (group F) or did not sustain (group NF) hip fracture by SOS *T*-score in accordance with WHO criteria for bone mineral density *T*-score (p<0.001). Decimals of the percentage points have been omitted.

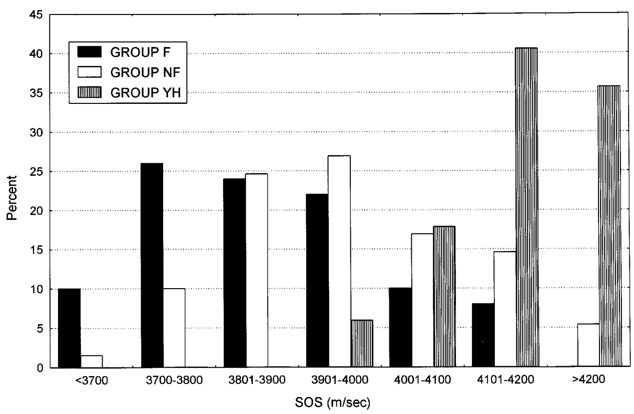

Fig. 5. Frequency distribution of elderly women who sustained (group F) or did not sustain (group NF) a hip fracture and young controls (group YH) according to speed of sound (SOS) measured at the radius.

Discussion

Our data reveal that SOS measured at the distal third of the radius by Omnisense discriminates between elderly women who had or had not sustained a proximal hip fracture. The OR discriminating hip fracture by SOS was lower using the full model (BMI- and age-adjusted) compared with the reduced (unadjusted) model. On the contrary, the AUC was higher using the full model compared with the reduced model. Although the full model results are not statistically different from the reduced model characteristics, these opposing trends may result from reporting the net effect of SOS on hip fracture by OR, which is reduced when other confounding factors are taken into account, while the AUC takes into account all the variables in the model employed, with more variables resulting in a higher discrimination. Our OR and AUC data are considerably lower than those reported using the prototype Omnisense version [6]. The diverting data are possibly related to younger age and higher mean BMI of the control women in the earlier study. These confounding variables are associated with higher SOS in the controls and thereby increase the difference from women who sustained hip fracture.

Several reports indicate that QUS measurement of bone determines acquired rather than inherited bone properties [8,9] and is superior to spine DXA but similar to hip DXA [10] in predicting hip fractures. As QUS systems do not use ionizing radiation, and are usually portable and cheaper than DXA, their use is gaining popularity in the diagnosis of osteoporosis [2–4]. One of the major drawbacks of using QUS devices is their limitation to measurement of a single skeletal site in face of nonuniform skeletal involvement in osteoporosis [5]. The ability of Omnisense to determine SOS at several peripheral skeletal sites is therefore of interest [6].

Our data, which linked hip fracture to low SOS values at the radius, are in agreement with many cross-sectional [11,12] and a few prospective [13,14] studies relating low SOS at the calcaneus to hip fracture. However, some reports claim no contribution of QUS at calcaneus in addition to hip DXA in determining the risk for hip fracture and spine osteopenia [15].

Our data for discrimination of proximal hip fracture by SOS, expressed in terms of an area under the ROC curve of 0.79, are in agreement with previous studies measuring SOS at the calcaneus [10,16] but higher than those measuring SOS at the tibia [5,6]. When expressed as OR, the current data are also in accordance with others relating low calcaneal SOS and fragility fracture risk [14,17].

In this study we did not include BMD data nor did we refer to the type of hip fracture. Therefore, it is interesting to note that recent studies indicate that QUS was better than spine DXA [10] in assessing hip fracture and distinguishing between trochanteric and cervical hip fractures [18].

Most of the QUS systems that employ transmission mode relate hip fracture risk to broadband ultrasound attenuation (BUA), probably because it is independent of soft tissue size and is highly correlated with calcaneal BMD. The major drawback of BUA determination is the relatively high measurement error [4], and its bone size dependence. The 'axial transmission' and the critical angle concept used by Omnisense allow high-precision measurement of SOS at various bone shapes and soft tissue thicknesses [18]. So far, as Omnisense does not determine BUA, it is not possible to compare SOS and BUA in fracture discrimination by this device. It is worthwhile noting that a related method of ultrasound that uses critical angle reflectometry is linked to nonelasticity independently of bone mass [19]. It thus supports the additional role of QUS in bone assessment [4]. Finally, there is currently no consensus for interpreting QUS in classification and diagnosis of osteoporosis [3]. It is interesting that the distribution of SOS *T*-scores in our patients who did not sustain a proximal hip fracture is similar to that of BMD determined by DXA [20].

This study has several overt limitations. The time since fracture of up to 9 years is a major limitation. Lower SOS in group F might in part be due to the lower physical activity in this group. The mean age was higher and mean BMI was lower in group F compared with group NF. Indeed the regression analysis indicates that aging and low BMI, independently of sustaining hip fracture, are associated with low SOS. The effect of BMI may be direct on bone ultrasound properties or through slowing ultrasound transmission within the thickened subcutaneous tissue. It is, therefore, possible that if adjustment for age and BMI is not perfect these confounding variables contribute to fracture discrimination independently of SOS. In addition, as the Omnisense is a multi-site device, it is possible that the hip fracture discrimination may be even better by combining data from several sites. This was indeed suggested using the prototype [6]. As a rule, a cross-sectional study can only discriminate hip fracture or estimate fracture risk but not evaluate risk for future fractures. Certainly, among those with low SOS in group NF there are women who may sustain a hip fracture should they be subject to a fall of sufficient energy. Therefore the AUC can never reach a value close to 1.0. In conclusion, our data indicate that SOS measured at the radius by the Omnisense discriminates patients with hip fracture. Prospective data are required to determine the role of Omnisense in assessing hip fracture risk.

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