Fracture Status in Men Assessed by Quantitative Ultrasound Measurements at the Calcaneus

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Objectives—The aim of the study was to assess fracture status in men by quantitative ultrasound measurements at the calcaneus. The diagnostic accuracy of quantitative ultrasound measurements was evaluated at baseline and follow-up.

Methods—We observed 165 men (baseline age ± SD, 59.84 ± 10.6 years) recruited from an outpatient osteoporosis clinic. The mean follow-up duration was approximately 101.3 ± 35 months. There was no difference in either age or body mass index at baseline between the patients with a fracture history (n = 30) and the others (n = 135). The following fractures were identified at baseline: ankle, 15; wrist, 10; rib, 9; foot, 5; and hip, 1. The speed of sound (meters per second), broadband ultrasound attenuation (decibels per megahertz), and stiffness index (percent) were measured with a quantitative ultrasound device. The date of fracture occurrence at follow-up was defined as the final point.

Results—In the patients with a fracture history, the ultrasound variables were significantly lower than those in the rest of the group ($P < .05$). During the follow-up period, fractures occurred in 21 patients (wrist, 11; ankle, 5; rib, 3; hip, 1; and humerus, 1), and the ultrasound outcomes were nonsignificantly lower in the fractured men. The risk of fracture was estimated by the Cox regression analysis. A prior fracture was the only factor that significantly (4 times) increased the risk of a subsequent fracture (hazard ratio, 4.21; 95% confidence interval, 1.81–9.86; $P < .001$).

Conclusions—Calcaneus ultrasound measurements can distinguish between patients with fractures and those without. In follow-up, ultrasound measurements did not indicate an increased fracture risk; a prior osteoporotic fracture was the major prognostic factor.

Key Words—fracture discrimination; fracture prediction; male; osteoporotic fracture; quantitative ultrasound

Nowadays, dual-energy x-ray absorptiometry (DXA) is the most common method for assessment of bone status and is considered the reference standard for bone densitometry. Using DXA, it is possible to measure the calcium content in the skeleton, defined as bone mineral density (BMD). A low BMD index is generally recognized as one of the most important fracture risk factors.[1] However, BMD measurements do have some disadvantages: they provide only quantitative information regarding bone tissue, and the sizes of measured bones affect the ultimate BMD value as displayed on a densitometer. The equipment used for such screening procedures is relatively expensive. More recently, some alternative methods of bone condition evaluation have been introduced, including quantitative ultrasound measurements.[2]

Received December 6, 2010, from the Metabolic Bone Diseases Unit (W.P.) and Department of Pathomorphology (B.D.), Medical University of Silesia, Zabrze, Poland; Departments of Orthopedics and Traumatology (R.W.) and Cardiology (K.S.G.), Medical University of Silesia, Katowice, Poland; and Regional Specialist Hospital No. 4, Bytom, Poland (A.W.). Revision requested December 28, 2010. Revised manuscript accepted for publication February 28, 2011.

We thank Paulina Goryl for assistance with manuscript preparation.

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Abbreviations
AUC, area under the curve; BMD, bone mineral density; DXA, dual-energy x-ray absorptiometry; ROC, receiver operating characteristic

The calcaneus is the most common site of ultrasound measurements for BMD assessment simply because of its easy availability, trabecular bone abundance, and weight-bearing resistance.[3] Because of its high turnover rate, cancellous bone shows tissue changes earlier than cortical bone. Most previous clinical studies on the matter were performed in women, distinguishing between the data in women with fractures and those in the rest of the study groups.[4–6] Several prospective studies have also shown that calcaneal quantitative ultrasound measurements predict osteoporotic fractures in women.[7–11] Nowadays, both DXA and quantitative ultrasound play important roles in terms of bone health and provide complementary clinical data.

The number of studies using quantitative ultrasound measurements in men is much smaller than the number of studies in women. In some cross-sectional studies, quantitative ultrasound variables were associated with a history of osteoporotic fractures in men,[12–14] and the estimated fracture risk was very close to that in women, as shown in studies performed with both sexes.[15,16] In certain studies, calcaneal quantitative ultrasound measurements were also successfully applied in natural menopause versus surgically induced menopause, in bronchial asthma, and in patients with mineral disorders.[17–19]

Obviously, the most reliable fracture risk predictions are provided by longitudinal studies. To the best of our knowledge, only 4 reports from longitudinal studies of calcaneal quantitative ultrasound predictive measurements have been published in the medical literature to date.[10,20–22] Recently, in a sample of men and women from the European Prospective Investigation Into Cancer–Norfolk study, who had both heel quantitative ultrasound and hip DXA measurements, it was shown that the predictive power of quantitative ultrasound measurements regarding fractures in the elderly was at least comparable to that of DXA.[23] Adding quantitative ultrasound measurements to models based on clinical risk factors and BMD values improves their predictive power, suggesting that quantitative ultrasound can become a useful clinical tool in fracture risk assessment.[24]

In this study, Polish men were evaluated by calcaneal quantitative ultrasound. The aim of the study was to assess fracture status in men. The diagnostic accuracy of quantitative ultrasound measurements was evaluated at baseline (comparison of fractured and nonfractured patients) and follow-up (comparison of fractured and nonfractured patients and assessment of fracture risk).

Materials and Methods

At baseline, the study included 374 men. They underwent ultrasound measurements at the calcaneus as part of their standard care in an outpatient osteoporotic clinic between 1993 and 2000. The patients had no disease histories (eg, hyperparathyroidism, thyroid gland diseases, chronic liver or kidney diseases, stomach surgery, and prolonged immobilization) or medication intake (eg, corticosteroids, thyroid hormones, anticonvulsants, and antacids) that could have affected bone metabolism. The enrolled patients were not treated for osteoporosis either at the time of the study or previously.

To gather data for fracture prognosis, 2 authors (R.W. and A.W.) prospectively telephoned the baseline group to determine the fracture status from the baseline quantitative ultrasound measurements until the day of the call. A total of 174 men were available by telephone, but 9 with spine fracture were excluded, leaving a study population of 165 men. (We had no access to patient radiographs, and the diagnosis of spine fractures was not sufficiently reliable.) Because of the retrospective study design, we were unable to properly evaluate physical activity, smoking, and alcohol and caffeine intake; thus no such information was included. We also did not collect information on weight and height at follow-up. All of the fractures at baseline and follow-up appeared to have resulted from low trauma: a fall from standing or lower height during normal daily activity. The clinical characteristics at baseline are presented in Table 1.

The study received approval from the local Ethics Committee, and informed consent was obtained from all patients.

Table 1. Clinical Characteristics at Baseline

Characteristic	Total (n = 165)	Nonfractured (n = 135)	Fractured (n = 30)	*P*
Age, y	56.3 ± 10.3	57.7 ± 10.5	60.3 ± 10.6	.218
Weight, kg	78.9 ± 11.8	81.1 ± 13.9	78.5 ± 11.0	.268
Height, m	1.71 ± 0.06	1.71 ± 0.06	1.71 ± 0.06	.852
Body mass index, kg/m^2	26.6 ± 3.4	27.5 ± 4.1	26.8 ± 3.3	.283

Values are mean ± SD. $P < .05$ was considered statistically significant.

Measurements

The evaluation of the skeletal status was based on quantitative ultrasound calcaneus measurements in the dominant extremity. In cases with a lower extremity fracture history, the opposite calcaneus was measured. The speed of sound (meters per second) and broadband ultrasound attenuation (decibels per megahertz) were measured with a Lunar Achilles quantitative ultrasound device (GE Healthcare, Madison, WI), which also additionally calculated the stiffness index (percent).

The device was calibrated daily in accordance with the manufacturer's recommendations. All of the measurements were done by the same operator, and their reproducibility was assessed by the use of a polyurethane phantom and on the basis of in vivo measurements. Fifteen phantom measurements, collected for 15 days, allowed calculation of short-term in vitro coefficients of variation: 0.12% for the speed of sound and 1.23% for broadband ultrasound attenuation. Long-term in vitro coefficients of variation were obtained from 20 phantom screening measurements over 4 years. They were 0.88% for the speed of sound and 0.54% for broadband ultrasound attenuation. Short-term in vivo precision was established from 60 measurements in 12 healthy men aged 23 to 66 years (5 in each of them). These coefficients of variation were 2.48% for broadband ultrasound attenuation and 0.33% for the speed of sound.

Statistical Analysis

Statistical analysis was performed with SPSS version 14.0.2 software (SPSS Inc, Chicago, IL) and MedCalc version 11.1.1.0 software (MedCalc, Mariakerke, Belgium). Data are presented as mean ± SD. Comparisons of baseline values between the patients with a fracture history and those with no fracture history were made with a 2-sample *t* test. To determine criterion values for the speed of sound, broadband ultrasound attenuation, and the stiffness index that distinguished patients with and without fracture histories, receiver operating characteristic (ROC) curves were generated, and the areas under the curves (AUCs) were calculated. We defined the criterion value as the one with the highest accuracy, ie, minimal false-negative and -positive results. Sensitivity and specificity were reported for each criterion value.

Cox proportional hazards modeling allows analysis of the effect of several risk factors on an outcome independent of an event. In this study, the event was defined as an osteoporotic fracture. We used Cox regression to assess the impact of separate predictors on the actual patients' outcomes independent of fractures. Variables entered into the initial model included the baseline age, weight, height, presumptive prior fracture, and quantitative ultrasound variables (speed of sound, broadband ultrasound attenuation, and stiffness index). $P < .05$ was considered statistically significant.

Results

Of the 165 patients in our study population, the mean duration of follow-up was 101.3 ± 35 months. At baseline, the mean age and body size in the patients with prior fractures (n = 30) did not differ from those in the rest of the group (n = 135). At baseline, the following fractures were noted: ankle, 15; wrist, 10; rib, 9; foot, 5; and hip, 1.

A comparison of baseline quantitative ultrasound values showed significantly lower values in the men with fractures (Table 2).

Figures 1–3 show ROC curves for the speed of sound, broadband ultrasound attenuation, and the stiffness index, respectively. A perfect screening tool that correctly classifies individuals into a pathologic (fractured) or normal (nonfractured) state would have an AUC estimate of 1.0, whereas a tool with no apparent accuracy would have an AUC estimate of 0.5.[21] The AUCs were 0.694 for the speed of sound ($P < .0001$), 0.638 for broadband ultrasound attenuation ($P < .01$), and 0.691 for the stiffness index ($P < .001$). The relevant cutoff values were as follows: 1503.6 m/s (sensitivity, 70%; specificity, 68%), 107.1 dB/MHz (sensitivity, 56.7%; specificity, 70.4%), and 83% (sensitivity, 83.3%; specificity, 49.6%). There were no statistically significant differences between AUCs for the speed of sound, broadband ultrasound attenuation, and the stiffness index.

During the follow-up period, the following fractures occurred in 21 men (12.7%): wrist, 11; ankle, 5; rib, 3; hip, 1; and humerus, 1. Of those patients, 9 had not had any fractures before (6.7%), and the remaining 12 fractures were recorded in patients with fractures at baseline (40%). During the follow-up period, age did not differ between the fractured and nonfractured groups (58.7 ± 11.3 versus

Table 2. Quantitative Ultrasound Results at Baseline

Parameter	Nonfractured (n = 135)	Fractured (n = 30)	*P*
Speed of sound, m/s	1525.7 ± 36.2	1502.6 ± 20.1	<.01
Broadband ultrasound attenuation, dB/MHz	113.1 ± 11.0	107.3 ± 11.4	<.05
Stiffness index, %	83.2 ± 16.2	72.6 ± 13.9	<.01
T-score	–1.57 ± 1.44	–2.32 ± 1.54	<.05
Z-score	–0.33 ± 1.4	–1.23 ± 1.24	<.01

Values are mean ± SD. $P < .05$ was considered statistically significant.

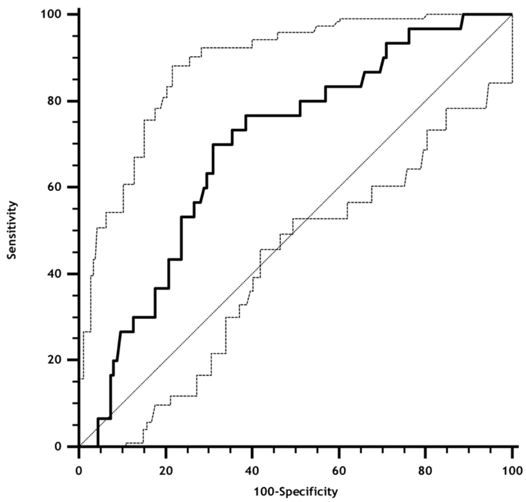


Figure 1. Receiver operating characteristic curve for the speed of sound (solid line) with 95% confidence limits (broken lines) measured at the baseline in patients with or without prior fracture.

60.0 ± 10.5 years, respectively). The ultrasound variables were nonsignificantly lower in the fractured men than in the previously nonfractured men (data not shown).

Cox analysis revealed that the risk of a fracture during follow-up was only significantly related to a fracture history (hazard ratio, 4.21; 95% confidence interval, 1.81–9.86; $P < .001$).

Discussion

The most important result of this study was that a fracture history was the only factor that significantly increased the actual fracture risk. That finding confirms several observations that a history of osteoporotic fractures is an important risk determinant for possible subsequent fractures.[1,25]

To our surprise, we also noticed certain adverse events, an inability of quantitative ultrasound measurements to predict fractures in longitudinal observations, which stood in contrast to the baseline comparison of quantitative ultrasound values in the fractured men and the others. Any fracture history was the only factor that significantly increased the fracture risk. At baseline, opposite results were obtained, and all of the quantitative ultrasound parameters were significantly lower in men with prior fracture. At baseline, the study showed diagnostic accuracy that was consistent with the results of other authors, confirming that quantitative ultrasound measurements at the calcaneus discriminate fractured from nonfractured men.[12–14] The AUCs obtained in this study were comparable to those obtained in our previous research (0.665 for broadband ultrasound attenuation and 0.706 the for speed of sound).[12] However, they were lower than those presented by other authors.[13,14] For instance, in a group of 102 men measured by the same device, Mulleman et al[13] obtained AUCs of 0.69 for broadband ultrasound attenuation, 0.75 for the speed of sound, and 0.74 for the stiffness index. In addition, the values in a study by Gonelli et al,[14] performed in

Figure 2. Receiver operating characteristic curve for broadband ultrasound attenuation (solid line) with 95% confidence limits (broken lines) measured at the baseline in patients with or without prior fracture.

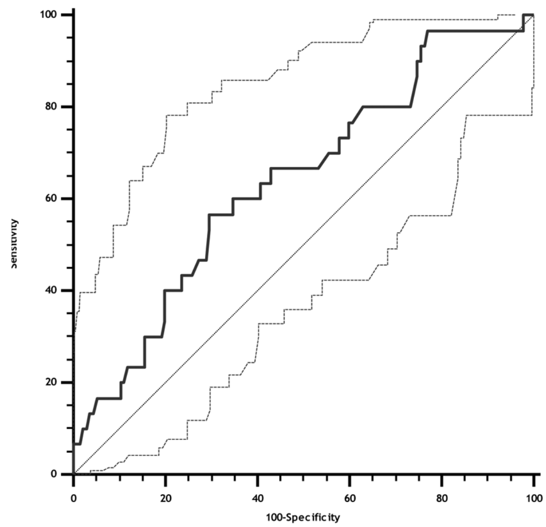
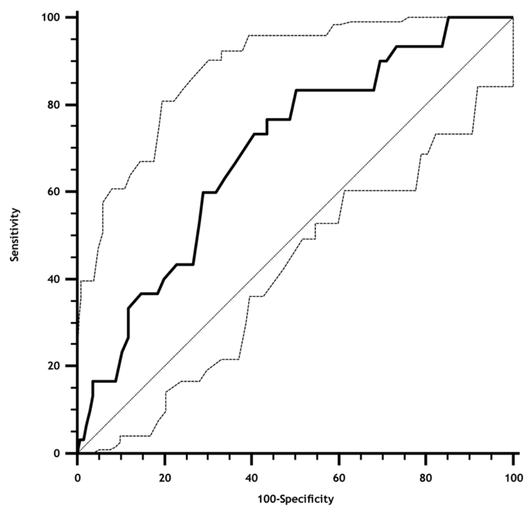


Figure 3. Receiver operating characteristic curve for the stiffness index (solid line) with 95% confidence limits (broken lines) measured at the baseline in patients with or without prior fracture.



401 men, were 0.72, 075, and 0.75, respectively, which did not coincide with our results at all.

Longitudinal studies performed in men to date have shown that calcaneal quantitative ultrasound measurements are adequate for evaluating fracture risks. In our study, we failed to confirm the utility of these measurements in predicting osteoporotic fractures.[10,20–22] There are several potential explanations for our results: first, exclusion of patients with spine fractures could possibly have affected the results; second, in the studied men, the main role was presumably played by another risk factor (eg, falls); third, it was possible that the telephone interviews could have been inaccurate in some cases because of verbal misunderstandings; and, finally, the number of fractures recorded in our study was lower than those reported by other researchers in the same field. To illustrate the discrepancy in other longitudinal studies, they reported the following numbers of fractures: 33,[21] 50,[22] and 239.[20]

A fracture in history is one of most important risk factors for subsequent fractures.[1,25] It appears then that one might expect that a patient with a fracture at baseline is also prone to have another fracture during a longitudinal observation period. The study results confirm these expectations: only 9 fractures were noted in the previously nonfractured men (7%), and the remaining 12 fractures were seen in those with fractures at baseline (40%). The general incidence of fractures in men is lower than that in women, and the numbers observed in our study population (18% at baseline and 14.6% at follow-up) were comparable to those of other authors.

In a prospective study, Pluijm et al[10] confirmed that a prior fracture was a determinant of a subsequent fracture (1.6 risk increase). In a prospective study performed in almost 15,000 men and women, a prior fracture increased the risk of a subsequent fracture to 3.53, which corresponded to our result of 4.2.[21] In another longitudinal study conducted in a male population, the authors disregarded fracture histories.[22]

This study had several limitations: our data were collected retrospectively, which may not have been as precise as in a prospective study; most of the patients evaluated at baseline were not available afterward; the number of fractures investigated was small; and patients with spine fractures were excluded. We cannot certainly rule out the possibility that spine fractures without symptoms were present in some cases during follow-up, which obviously could not be diagnosed or taken into consideration.

In conclusion, calcaneus ultrasound measurements can distinguish between patients with fractures and those without. During follow-up, ultrasound measurements did not indicate an increased fracture risk; a prior osteoporotic fracture was the major prognostic factor.

References

1. Nguyen ND, Frost SA, Center JR, Eismann JA, Nguyen TV. Development of prognostic nomograms for individualizing 5-year and 10-year fracture risks. *Osteoporos Int* 2008; 19:1431–1444.
2. Gregg EW, Kriska AM, Salamone LM, et al. The epidemiology of quantitative ultrasound: a review of the relationships with bone mass, osteoporosis and fracture risk. *Osteoporos Int* 1997; 7:89–99.
3. Vogel J, Wasnich R, Ross P. Clinical relevance of calcaneus bone mineral measurement: a review. *Bone Miner* 1988; 5:35–58.
4. Massie A, Reid DM, Porter RW. Screening for osteoporosis: comparison between dual energy X-ray absorptiometry and broadband ultrasound attenuation in 1000 perimenopausal women. *Osteoporos Int* 1993; 3:107–110.
5. Yamazaki K, Kushida K, Ohmura A, Sano M, Inoue T. Ultrasound bone densitometry of the os calcis in Japanese women. *Osteoporos Int* 1994; 4:220–225
6. Drozdzowska B, Pluskiewicz W. The ability of quantitative ultrasound at the calcaneus to identify postmenopausal women with different types of nontraumatic fractures. *Ultrasound Med Biol* 2002; 28:1491–1497.
7. Porter RW, Miller CG, Grainger D, Palmer SB. Prediction of hip fracture in elderly women: a prospective study. *BMJ* 1990; 301:638–641.
8. Hans D, Dargent-Molina P, Schott AM, et al. Ultrasonographic heel measurements to predict hip fracture in elderly women: the EPIDOS prospective study. *Lancet* 1996; 348:511–514.
9. Bauer DC, Gluer CC, Cauley JA, et al. Broadband ultrasound attenuation predicts fractures strongly and independently of densitometry in older women: a prospective study. Study of Osteoporotic Fractures Research Group. *Arch Intern Med* 1997; 157:629–634.
10. Pluijm SMF, Graafmans WC, Bouter LM, Lips P. Ultrasound measurements for the prediction of osteoporotic fractures in elderly people. *Osteoporos Int* 1999; 9:550–556.
11. Huopio J, Kröger H, Honkanen R, Jurvelin J, Saarikoski S, Alhava E. Calcaneal ultrasound predicts early postmenopausal fractures as well as axial BMD: a prospective study of 422 women. *Osteoporos Int* 2004; 15:190–195.
12. Pluskiewicz W, Drozdzowska B. Ultrasound measurements at the calcaneus in men: differences between healthy and fractured persons and the influence of age and antropometric features on ultrasound parameters. *Osteoporos Int* 1999; 10:47–51.
13. Mulleman D, Legroux-Gerot I, Duquesnoy B, Marchandise X, Delcambre B, Cortet B. Quantitative ultrasound of bone in male osteoporosis. *Osteoporos Int* 2002; 13:388–393.
14. Gonelli S, Cepollaro C, Gennari L, et al. Quantitative ultrasound and dual-energy X-ray absorptiometry in the prediction of fragility fracture in men. *Osteoporos Int* 2005; 16:963–968.
15. Pluskiewicz W, Drozdzowska B. Ultrasonic measurement of the calcaneus in Polish normal and osteoporotic women and men. *Bone* 1999; 24:611–617.

16. Maggi S, Noale M, Giannini S, et al. Quantitative heel ultrasound in a population-based study in Italy and its relationship with fracture history: the ESOPO study. *Osteoporos Int* 2006; 17:237–244.
17. Drozdzowska B. Quantitative ultrasound measurements at the calcaneus in natural and surgically induced menopause. *Maturitas* 2006; 53:107–113.
18. Drozdzowska B. Skeletal status assessed by quantitative ultrasound at the calcaneus in females with bronchial asthma on prolonged corticosteroid therapy. *Maturitas* 2005; 51:386–392.
19. Pluskiewicz W, Pyrkosz A, Drozdzowska B, Halaba Z. Quantitative ultrasound of the hand phalanges in patients with genetic disorders: a pilot case-control study. *Osteoporos Int* 2003; 14:787–792.
20. Bauer DC, Ewing SK, Cauley JA, Ensrud KE, Cummings SR, Orwoll ES; Osteoporotic Fractures in Men (MrOS) Research Group. Quantitative ultrasound predicts hip and non-spine fracture in men: the MrOS study. *Osteoporos Int* 2007; 18:771–777.
21. Khaw KT, Reeve J, Luben R, et al. Prediction of total and hip fracture risk in men and women by quantitative ultrasound of the calcaneus: EPIC-Norfolk prospective population study. *Lancet* 2004; 363:197–202.
22. Fujiwara S, Sone T, Yamazaki K, et al. Heel bone ultrasound predicts non-spine fracture in Japanese men and women. *Osteoporos Int* 2005; 16:2107–2112.
23. Moayyeri A, Kaptoge S, Dalzell N, et al. The effect of including quantitative heel ultrasound in models for estimation of 10-year absolute risk of fracture. *Bone* 2009; 45:180–184.
24. Moayyeri A, Kaptoge S, Dalzell N, Bingham S, Luben RN, Wareham NJ, Reeve J, Khaw KT. Is QUS or DXA better for predicting the 10-year absolute risk of fracture? *J Bone Miner Res* 2009;24:1319-1325.
25. Kanis JA, Johnell O, Oden A, Johansson H, McCloskey E. FRAX and the assessment of fracture probability in men and women from the UK. *Osteoporos Int* 2008; 19:385–397.