Discriminative ability of calcaneal quantitative ultrasound compared with dual-energy X-ray absorptiometry in men with hip or distal forearm fractures

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Abstract

Objectives: The aim of this case–control study was to compare the discriminatory ability of bone mineral density (BMD) measurements and calcaneal quantitative ultrasound (QUS) parameters for fractures and to determine fracture thresholds for each variable in men with hip or distal forearm fractures.

Patients and methods: A total of 20 men with hip and 18 men with distal forearm fractures and 38 age-matched controls were included in this study. Dual-energy X-ray absorptiometry (DXA) BMD (spine and hip) and calcaneal QUS measurements were made. Area under the curves (AUCs) were calculated to assess fracture discriminatory power of DXA and QUS variables.

Results: Quantitative Ultrasound Index (QUI) T-score and Speed of Sound (SOS) were found to be the best parameters for the identification of hip and distal forearm fractures, respectively, with AUCs greater than those of DXA BMD and other QUS parameters. While a QUI T-score of 1.18 could identify and rule out hip fracture cases with approximately 80% sensitivity and specificity, a SOS value of 1529.75 reached to almost 90% for ruling in and out distal forearm fractures.

Conclusion: The discriminatory performance of calcaneal QUS variables between fractured and non-fractured men was as good as those of the DXA BMD and even better. Since men appear to sustain fractures at closer QUS variable levels than those of the DXA BMD regardless of the fracture type, it may be speculated that calcaneal QUS may be more helpful in predicting the risk of fractures when BMD alone does not demonstrate impaired bones.

Level of Evidence: Level III, Study of Diagnostic Test

Introduction

The most common osteoporotic fractures include distal forearm fractures (DFFs), hip fractures (HFs), and vertebral fractures with an estimated number of 1.7, 1.6, and 1.4 million, respectively, in 2000.1 The remaining life-course probability of a HF and a DFF at age 50 was estimated as 10.7% and 22.9% in men, respectively.2

The association between HFs and mortality is well established in both genders, being higher in males.3 Increasing evidence also suggests an increased risk for premature mortality in those with DFFs.3 Osteoporotic fractures may also cause significant disability2 as well as tremendous societal and economic impact.1 Therefore, it is crucial to predict the risk of osteoporotic fractures and/or to identify bone characteristics of fractureurs to apply evidence-based pharmacological and non-pharmacological treatment options for prevention.5,6

While dual energy X-ray absorptiometry (DXA) bone mineral density (BMD) measurement is the gold standard for predicting HFs,7 two meta-analyses of prospective studies showed that calcaneal quantitative ultrasound (cQUS) variables were strong predictors of non-spinal fracture risk, in both men and women usually in a way comparable to DXA-BMD measurements.8,9 cQUS studies are not as many as in men than they are in women.9 A number of case–control studies provided evidence on the fracture discriminatory ability of cQUS in men10–14 however, very few of them assessed cut-off values for QUS variables for fractures providing us with any osteoporotic fracture thresholds while not defining separate cutoff points for HFs or DFFs.15,16
The aim of this case-control study was two-fold: to compare the fracture discriminatory ability of cQUS parameters and DXA-BMD measurements and to determine fracture thresholds for DXA-BMD and cQUS variables separately for HF or DFFs in men.

**Patients and methods**

**Participants**

The study participants consisted of 38 men with low-energy fractures in the period of 6 months after fracture, 20 having HF and 18 having DFFs and 38 age-matched men (±2 years than each fracture) without any fracture, disease, or medications known to affect bone metabolism as the control group. All of the subjects filled out a questionnaire including information such as age, height and weight, handedness, smoking status, physical activity level (the time spent for walking before the fracture categorized as <1, 1–2, and >2 h a week), a family or own history of osteoporotic fracture, and information for fractures such as type and side of fracture, and time since fracture. Participants had cQUS and DXA-BMD measurements. The study protocol was approved by the local Ethics Committee and written informed consent was obtained from all of the participants.

**DXA measurements**

DXA-BMD measurements were made using a Hologic QDR 1000 DXA device (Hologic, Waltham, MA, USA) at posteroanterior spine and hip (at the non-fractured side in the fracture and at the nondominant side in the controls). Hip fractured men were ambulatory, being able to come to our bone densitometry unit for testing. The BMD of the vertebral from L1 to L4 at the lumbar spine (LS) and femoral neck (FN), and total femur BMD at the hip were included in the data analysis. The presence of osteoporosis at any region of interest (ROI) was defined as a T-score ≤−2.5. A T-score between −1 and −2.5 was classified as low bone mass/osteopenia and a T-score ≥−1 was classified as normal.17 However, Z-scores of ≤−2.0 were used for defining BMD “below the expected range for age,” (osteoporosis), while Z-scores >−2.0 were considered “within the expected range for age” (normal) in those <50 years.18 An individual was considered as osteoporosis in the presence of a T-score ≤−2.5 or a Z-score ≤−2.0 (<50 years) in any of the ROIs.

**QUS measurements**

Acoustic parameters of bone were measured using a portable, gel-coupled cQUS device (Sahara® Clinical Bone Sonometer, Hologic, Waltham, MA, USA). This device measures broadband ultrasound attenuation (BUA) (dB/MHz) and the speed of sound (SOS) (m/s) and calculates Quantitative Ultrasound Index (QUI) as well as a QUI T-score and estimated heel BMD (eBMD) (g/cm²). Daily quality control was performed using a phantom provided by the manufacturer. Given the findings that considerable differences may exist between sides as found in women19 both heel measurements were made and repeated with repositioning of the feet. The mean of the two measurements were calculated for both feet and the lowest mean value of QUS variables obtained for the two sides was included in statistical analyses, except for the hip fractured men in whom the mean of QUS measurements of the non-fractured side was used.

**Precision of cQUS parameters**

The short-term precision of the QUS variables was examined as recommended by Glüer et al using the double measurements obtained in all subjects with repositioning of the feet as the root-mean-square coefficient of variation (RMS-%CV) according to the following formula: \( \text{RMS-%CV} = \sqrt{\frac{\text{CV}^2}{n}} \times 100 \) (CV: coefficient of variation).20

**Statistical analysis**

For statistical analyses, SPSS software, version 17.0 (SPSS Inc., Chicago, IL, USA) was employed. We used Student’s t-test and Chi square tests to compare continuous and dichotomous variables, respectively, in fracture and non-fracture subjects. Receiver operating characteristic (ROC) analysis was used to determine fracture discriminatory ability of QUS and BMD variables. Areas under the ROC curves (AUCs) were calculated for each variable. The sensitivity and specificity of various cut-off points for each variable in ROC curves showing the best balance were used to determine fracture thresholds for variables. Significance was set at \( p < 0.05 \).

**Results**

One participant with a HF and a HF control did not have a spine BMD measurement due to metal implants in one and positioning difficulties in the other. A man with a HF and the other with a DFF did not have a hip DXA measurement due to positioning problems. Characteristics of study participants are shown in Table 1. BMD and QUS variables are displayed in Table 2. AUCs are given in Table 3. Various cut-off values for BMD and QUS variables and their sensitivity and specificity are shown in Table 4. The precision of QUS variables are shown in Table 5.

**Discussion**

As expected, the results of this study revealed significantly lower values for both DXA-BMD and cQUS variables in those with fractures when compared with those without (Table 2) in line with other studies comparing DXA and QUS variables for the identification of hip,11,21,22 lower extremity,14 or all osteoporosis-related fractures.23,24 Studies using only QUS in men also demonstrated significantly lower QUS variables in fracture than nonfractures.10,12,13,15,16

The ability of DXA-BMD measurements in separating men with HF or DFFs from those without could be considered as “fair” or “good” with AUCs ranging from 0.772 (for FN T-score) to 0.838 (for L1–L4 T-score) for HFs and 0.775 (for L1–L4 BMD) to 0.891 (for FN T-score) for DFFs (Table 3). It was interesting to note that discriminative power of L1–L4 BMD was higher than that of the FNBMD for HFs as reflected by AUCs (0.836 vs. 0.778) and vice versa for DFFs (0.775 vs. 0.876), despite the findings of a strong association with risk of HF, and FNBMD in men and weaker association with LSBMD.25 However, another study did show the equally good predictive ability of LS and FNBMD for various types of fractures in women.26 Supporting this finding, two studies in men with any osteoporotic fractures demonstrated a better discrimination power of LSBMD than that of FNBMD, AUC values for LS vs. FNBMD being 0.800 vs. 0.730 and 0.668 vs. 0.643, possibly resulting from the inclusion of relatively fewer number of men with non-spinal fractures. Whether these findings apply to HFs alone in men remains to be further investigated in large-scale prospective studies. As for DFFs, in parallel with our findings, FNBMD was found a significant risk factor.13,27,28

CQUS variables discriminated men with HF or DFFs in a way comparable to DXA-BMD measurements with similar or slightly greater AUCs varying from 0.819 (for BUA) to 0.841 (for QUI T-score), implying “good” discriminatory ability. For men with DFFs, all QUS variables, with the exception of BUA, could be considered as...
forearm fracture cases (p < 0.05).

Mean ± SD are shown for continuous variables; Number of participants (%) are shown for categorical variables as YES/NO; p values for variables for hip fracture vs. distal forearm fracture cases (p < 0.05).

Table 2

| BMD and QUS Variables in participants with hip or distal forearm fractures and controls. | Hip fracture (n. 20) | Controls (n. 20) | p value | Forearm fracture (n. 18) | Controls (n. 18) | p value | p value |
|---|---|---|---|---|---|---|---|
| L1–L4 BMD (g/cm²) | 0.845 ± 0.165 | 1.069 ± 0.145 | <0.001 | 0.899 ± 0.105 | 1.026 ± 0.102 | 0.001 | 0.235 |
| L1–L4 T-score | −2.23 ± 1.53 | −0.19 ± 1.32 | <0.001 | −1.78 ± 0.97 | −0.59 ± 0.97 | 0.001 | 0.286 |
| Femoral neck BMD (g/cm²) | 0.635 ± 0.111 | 0.794 ± 0.160 | 0.001 | 0.724 ± 0.103 | 0.876 ± 0.080 | <0.001 | 0.018 |
| Femoral neck T-score | −2.15 ± 0.86 | −1.03 ± 1.17 | 0.002 | −1.52 ± 0.75 | −0.33 ± 0.60 | <0.001 | 0.027 |
| Total hip BMD (g/cm²) | 0.757 ± 0.118 | 0.956 ± 0.176 | <0.001 | 0.856 ± 0.124 | 0.999 ± 0.086 | <0.001 | 0.019 |
| Total hip T-score | −1.81 ± 0.79 | −0.53 ± 1.16 | <0.001 | −1.18 ± 0.82 | −0.16 ± 0.56 | <0.001 | 0.024 |
| QUI | 75.90 ± 17.91 | 100.61 ± 17.38 | <0.001 | 73.67 ± 8.56 | 94.83 ± 13.68 | <0.001 | 0.624 |
| QUI T-score | −1.83 ± 1.02 | −0.47 ± 1.00 | <0.001 | −2.02 ± 0.53 | −0.77 ± 0.80 | <0.001 | 0.473 |
| BUA (dB/MHz) | 57.01 ± 20.03 | 79.99 ± 16.05 | <0.001 | 56.58 ± 8.87 | 74.26 ± 14.76 | <0.001 | 0.931 |
| SOS (m/s) | 1520.84 ± 24.80 | 1557.82 ± 28.16 | <0.001 | 1514.58 ± 13.97 | 1548.52 ± 20.03 | <0.001 | 0.339 |
| eBMD (g/cm²) | 0.404 ± 0.113 | 0.560 ± 0.110 | <0.001 | 0.388 ± 0.056 | 0.524 ± 0.086 | <0.001 | 0.579 |

DXA: dual-energy X-ray absorptiometry; BMD: Bone mineral density; QUS: Quantitative ultrasound; L1–L4: lumbar vertebrae 1 to 4; QUI: Quantitative ultrasound index; BUA: Broadband ultrasound attenuation; SOS: Speed of sound; eBMD: estimated heel BMD. Mean ± SD are shown for continuous variables; p values for variables for hip fracture vs. distal forearm fracture cases (p < 0.05).

Table 3

| Area under the ROC curves for fracture discrimination power of variables. |
|---|---|---|---|---|---|---|---|
| BMD and QUS Variables | Hip fracture | Distal forearm fracture |
| | Area | SE | p value | 95% CI | Area | SE | p value | 95% CI |
| L1–L4 BMD (g/cm²) | 0.836 | 0.066 | <0.001 | 0.708 | 0.065 | 0.001 | 0.775 | 0.078 | 0.006 | 0.621 | 0.928 |
| L1–L4 T-score | 0.838 | 0.065 | <0.001 | 0.710 | 0.065 | 0.001 | 0.788 | 0.076 | 0.004 | 0.639 | 0.936 |
| Femoral neck BMD (g/cm²) | 0.778 | 0.075 | 0.004 | 0.630 | 0.025 | 0.001 | 0.876 | 0.064 | <0.001 | 0.751 | 1.001 |
| Femoral neck T-score | 0.772 | 0.076 | 0.005 | 0.623 | 0.021 | 0.001 | 0.891 | 0.058 | <0.001 | 0.776 | 1.005 |
| Total hip BMD (g/cm²) | 0.822 | 0.068 | 0.001 | 0.689 | 0.094 | 0.001 | 0.827 | 0.073 | 0.001 | 0.684 | 0.970 |
| Total hip T-score | 0.801 | 0.072 | 0.002 | 0.660 | 0.042 | 0.001 | 0.851 | 0.068 | <0.001 | 0.718 | 0.985 |
| QUI | 0.836 | 0.067 | <0.001 | 0.704 | 0.068 | 0.001 | 0.918 | 0.046 | <0.001 | 0.829 | 1.008 |
| QUI T-score | 0.840 | 0.071 | <0.001 | 0.710 | 0.072 | 0.001 | 0.918 | 0.045 | <0.001 | 0.830 | 1.007 |
| BUA (dB/MHz) | 0.819 | 0.072 | 0.002 | 0.677 | 0.060 | 0.001 | 0.840 | 0.067 | 0.001 | 0.708 | 0.971 |
| SOS (m/s) | 0.825 | 0.069 | 0.001 | 0.689 | 0.061 | 0.001 | 0.938 | 0.042 | <0.001 | 0.856 | 1.019 |
| eBMD (g/cm²) | 0.836 | 0.067 | <0.001 | 0.704 | 0.068 | 0.001 | 0.922 | 0.044 | <0.001 | 0.835 | 1.008 |

ROC: Receiver operating characteristic; SE: Standard error; BMD: Bone mineral density; QUS: Quantitative ultrasound; L1–L4: lumbar vertebrae 1 to 4; QUI: Quantitative ultrasound index; BUA: Broadband ultrasound attenuation; SOS: Speed of sound; eBMD: estimated heel BMD. Mean ± SD are shown for continuous variables; p values for variables for hip fracture vs. distal forearm fracture cases (p < 0.05).
“excellent” in identifying fractured and non-fractured men with AUCs ranging from 0.840 (for BUA) to 0.938 (for SOS). While QUI T-score showed the best HF discriminative capability, SOS was found to have the highest AUC for the identification of any fracture in a study, another study showed greater AUCs for SOS (0.750) than that for FNBMD (0.730). Studies calculating RR or HR for fracture prediction also demonstrated varying results, the predictive ability of DXA-BMD being superior to QUS measurements in some studies and being identical for any NSFs and superior for HFs in another study. It seems that the results with regard to the discriminative ability of DXA BM in comparison to QUS measurements as well as those of the QUS parameters in comparison to each other are inconsistent across studies, possibly resulting from different QUS devices used in studies (technical differences among QUS devices known to affect values), diverse ethnicities and geographical differences (affecting BMD values), and being identical for any NSFs and superior for HFs in another study.

The most important feature of this study is the calculation of cut-off values for each DXA-BMD and QUS variable for HFs and DFFs (Table 4). A QUI T-score of \( t_{1.18} \) provided the best compromise between sensitivity and specificity with ~80% (for SOS) and ~78% (for BUA). While the discriminatory/predictive ability of DXA-BMD were similar with those of the QUS variables, AUCs ranging from 0.71 to 0.77 for BMD and 0.720 to 0.750 for QUS variables for the identification of any fracture in a study, another study showed greater AUCs for SOS (0.750) than that for FNBMD (0.730). Studies calculating RR or HR for fracture prediction also demonstrated varying results, the predictive ability of DXA-BMD being superior to QUS measurements in some studies and being identical for any NSFs and superior for HFs in another study. It seems that the results with regard to the discriminative ability of DXA BM in comparison to QUS measurements as well as those of the QUS parameters in comparison to each other are inconsistent across studies, possibly resulting from different QUS devices used in studies (technical differences among QUS devices known to affect values), diverse ethnicities and geographical differences (affecting BMD values), and being identical for any NSFs and superior for HFs in another study.

### Table 4

| BMD and QUS variables | Hip fracture | Distal forearm fracture |
|-----------------------|-------------|------------------------|
|                       | Cut-off values | Sensitivity | Specificity | Cut-off values | Sensitivity | Specificity |
| L1–L4 BMD (g/cm²)     | 0.954        | 0.667                  | 0.789       | 0.948         | 0.588       | 0.722       |
|                       | 0.966        | 0.722                  | 0.737       | 0.956         | 0.588       | 0.611       |
|                       | 0.984        | 0.778                  | 0.737       | 0.970         | 0.647       | 0.611       |
| L1–L4 T-score         | -1.26        | 0.667                  | 0.789       | -1.30         | 0.588       | 0.667       |
|                       | -1.14        | 0.722                  | 0.737       | -1.23         | 0.588       | 0.611       |
|                       | -0.97        | 0.778                  | 0.737       | -1.10         | 0.647       | 0.611       |
| Femoral neck BMD (g/cm²) | 0.673     | 0.556                  | 0.632       | 0.773         | 0.765       | 0.833       |
|                       | 0.679        | 0.611                  | 0.632       | 0.795         | 0.824       | 0.833       |
|                       | 0.684        | 0.667                  | 0.632       | 0.814         | 0.824       | 0.778       |
| Femoral neck T-score  | -1.30        | 0.556                  | 0.632       | -1.16         | 0.715       | 0.833       |
|                       | -1.85        | 0.611                  | 0.632       | -0.98         | 0.824       | 0.833       |
|                       | -1.81        | 0.667                  | 0.632       | -0.82         | 0.882       | 0.833       |
| Total hip BMD (g/cm²) | 0.799        | 0.667                  | 0.737       | 0.909         | 0.706       | 0.778       |
|                       | 0.812        | 0.667                  | 0.684       | 0.934         | 0.706       | 0.722       |
| Total hip T-score     | -1.39        | 0.611                  | 0.684       | -0.76         | 0.706       | 0.778       |
|                       | -1.32        | 0.611                  | 0.579       | -0.54         | 0.824       | 0.722       |
| QUI                    | 83.38        | 0.722                  | 0.779       | 81.50         | 0.765       | 0.833       |
|                       | 88.03        | 0.778                  | 0.779       | 81.95         | 0.765       | 0.778       |
|                       | 92.10        | 0.833                  | 0.779       | 82.33         | 0.824       | 0.778       |
|                       | -1.45        | 0.722                  | 0.779       | -1.58         | 0.765       | 0.833       |
|                       | -1.18        | 0.778                  | 0.779       | -1.53         | 0.765       | 0.778       |
|                       | -0.93        | 0.833                  | 0.779       | -1.45         | 0.882       | 0.778       |
| BUA (dB/MHz)           | 67.38        | 0.667                  | 0.737       | 63.85         | 0.706       | 0.778       |
|                       | 68.33        | 0.722                  | 0.776       | 64.87         | 0.765       | 0.778       |
|                       | 68.68        | 0.778                  | 0.776       | 65.55         | 0.765       | 0.722       |
| SOS (m/s)              | 1532.15      | 0.722                  | 0.779       | 1528.60       | 0.822       | 0.944       |
|                       | 1537.50      | 0.778                  | 0.779       | 1529.75       | 0.882       | 0.889       |
|                       | 1540.65      | 0.833                  | 0.779       | 1530.80       | 0.882       | 0.833       |
|                       | 1541.25      | 0.722                  | 0.779       | 0.439         | 0.765       | 0.778       |
|                       | 0.480        | 0.778                  | 0.779       | 0.442         | 0.765       | 0.778       |
|                       | 0.506        | 0.833                  | 0.779       | 0.445         | 0.824       | 0.778       |

BMD: Bone mineral density; QUS: Quantitative ultrasound; L1–L4: lumbar vertebrae 1 to 4; QUI: Quantitative ultrasound index; BUA: Broadband ultrasound attenuation; SOS: Speed of sound; eBMD: estimated heel BMD (Values providing the best compromise between sensitivity and specificity are marked in bold).

### Table 5

| QUI | BUA | SOS | eBMD |
|-----|-----|-----|------|
| Right heel | 2.73 | 5.33 | 0.26 | 3.17 |
| Left heel  | 2.76 | 5.85 | 0.25 | 3.08 |

QUS: Quantitative ultrasound; RMS CV: root-mean-square coefficient of variation; BMD: QUI: Quantitative ultrasound index; BUA: Broadband ultrasound attenuation; Bone mineral density; SOS: Speed of sound; eBMD: estimated heel BMD.
optimal cut-off levels were suggested as 1503.6 m/s for SOS and 107.1 dB/MHz for BUA in 30 individuals with various types of fractures\textsuperscript{15} which did not coincide with the cut-off values in our study. A cut-off level of \textasciitilde{}1.30 for SI T-score was suggested for the prediction of NSFs in Chinese men.\textsuperscript{33} The specificity and sensitivity of optimal cut-off values for the majority of QUS variables were higher than those of the DXA-BMD measurements for both types of fractures. An important finding of the present study was that both HFs and DFFs occurred at similarly relative smaller QUS thresholds relative to those of the DXA-BMD measurements except for L1–L4 BMD and T-score. This finding provides implications that cQUS may predict fractures earlier than DXA, an issue that needs clarification in large sampled-sized prospective studies.

The prevalence of osteoporosis in any ROI in men with HFs was 55.6\%; whereas, only 5.0\% of the controls was osteoporotic. In those with DFFs, the prevalence of osteoporosis was 38.9\%, while none in their controls. In parallel with our findings, a study found that while HFs were more common in men with osteoporosis, DFF rates were similar in those with osteopenia and osteoporosis.\textsuperscript{15} It appears that DFFs in men occur more often in the non-osteoporotic BMD range than those of HFs, the absence of osteoporosis not precluding the occurrence of osteoporosis-related fractures in men. Thus, prediction of DFFs relying on BMD values seems more difficult and necessitates an alternative tool for which QUS appears to be a good candidate.

The magnitude of precision errors for QUS variables (Table 5) was lower for SOS and QUI and higher for BUA than those found in other studies employing the Sahara\textsuperscript{®} in men\textsuperscript{22,24}

\textbf{Limitations of the study}

The results of this study should be interpreted cautiously due to some limitations. The smallness of the number of men with HFs and DFFs may make generalizability of the results difficult. This small sample size did not allow us to calculate definitive ORs for variables for their discriminative power, yielding wide confidence intervals creating uncertainty (data not shown). Additionally, the design of the study, not being prospective, may have weakened the predictive power of variables. Furthermore, QUS parameters may have been biased by physical activity level, which significantly differed between the fractured and non-fractured men, given the positive linear relationship of BUA and SOS with physical activity levels.\textsuperscript{33} It is also important to note that the measurement of DXA-BMD and QUS variables within 6 months after a hip fracture (mean post-fracture duration: 4.08 months) may have also contributed to lower BMD [shown to have been decreased after a hip fracture]\textsuperscript{34} and QUS values [shown to have been associated with physical activity]\textsuperscript{33} due to the immobilization period after hip surgery. However, considering the low level of physical activity in men before a HF, and the findings of a study demonstrating that current physical activity accounted for 14% of the variance in FNBMID in healthy middle-aged and older men,\textsuperscript{35} we may speculate that DXA-BMD and QUS measurements at a relatively shorter time after a HF may not have obscured substantial differences regarding the relevant variables between hip fractured and non-fractured men to a significant extent.

\textbf{Conclusions}

The results of this small-sample study demonstrated similar to or even better fracture discriminative performance of cQUS variables when compared with those of the DXA-BMD with the QUI T-score as the best parameter for the identification of HFs and SOS as the best parameter for the discrimination of DFFs. It is important to note that DFFs in men do occur at younger ages and at high BMD values, slightly weakening the discrimination performance of DXA. Since men appear to fracture hips or forearms at similar QUS variable levels, it may be speculated that cQUS may be more helpful in predicting the risk of fractures when BMD alone does not demonstrate impaired bones. Prospective studies with much larger sample sizes separately evaluating the association between cQUS and different types of fractures may elucidate the role of cQUS in predicting fractures with more definitive conclusions.

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