Advancing Methods of Assessing Bone Quality to Expand Screening for Osteoporosis

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Context: Dual-energy x-ray absorptiometry (DXA) limits osteoporosis screening because of machine size, technical requirements for operation, and exposure to ionizing radiation.

Objective: To establish data ranges from calcaneus ultrasonography (US) that correspond to bone mineral density (BMD) stratification identified by DXA and to determine whether vitamin D concentration adds to US bone health assessment.

Methods: Patients scheduled for DXA at the Robert C. Byrd Clinic, a rural primary care facility in Lewisburg, West Virginia, were recruited from June 2015 to June 2016. Ultrasonography was used to scan the left and right calcaneus of the patients, and blood was collected from a finger prick for vitamin D analysis. Information was collected regarding Fracture Risk Assessment tool parameters, menstrual history, and drug and supplement use. The correlations within and between DXA and US measurements were calculated, as well as the correlations between DXA and US measurements and vitamin D levels. Predictive performance of US readings on bone health determined by DXA scan was assessed with area under the curve analysis using receiver operator characteristic curves.

Results: Ninety-nine participants were included. Ultrasonography readings of either the left or right foot were predictive of good vs poor bone quality. No differences were found between US scans of the left foot vs the right foot. Area under the curve values for US BMD T scores for the left and right foot were 0.69 and 0.68, respectively. There was no correlation between DXA- and US-assessed BMD and vitamin D concentrations. Negative correlations were observed between the DXA BMD T scores and vitamin D concentration of the spine and right hip; negative correlations were also observed in the Z score from the spine in the subset of participants who reported not taking vitamin D supplements.

Conclusion: Ultrasonography of the calcaneus offers a low-cost, efficient means to screen bone health. The affordability and mobility of a US machine enables its use as a screening method that may be applicable to large numbers of people. This study established a T score greater than −1.05 as an indicator of good bone quality and a T score less than −1.05 as an indicator of poor bone quality when using US for BMD screening.


Keywords: bone mineral density, dual-energy x-ray absorptiometry, osteoporosis, ultrasonography
Osteoporosis is a disease of bone characterized by low bone mineral density (BMD) and microarchitectural deterioration, which leads to an increase in fragility and slower healing. According to the United States Preventive Services Task Force, it is estimated that 1 of every 2 women and 1 of every 5 men is at risk for an osteoporotic fracture during their lifetime. The economic burden of osteoporotic fractures has been estimated to be $12.2 to $17.9 billion per year in direct medical costs. History of an osteoporotic fracture is also associated with increased mortality—20% of people who have a hip fracture die within 6 months. Reducing the risk and occurrence of osteoporotic fractures is necessary to sustain and improve both the human and economic costs related to this disease.

Currently, osteoporosis is diagnosed using dual-energy x-ray absorptiometry (DXA). While effective in identifying individuals with low BMD, using DXA to screen for bone health is limited because of the cost, size, and technical needs required to operate the machine. Dual-energy x-ray absorptiometry also exposes patients to ionizing radiation, albeit very low levels. Therefore, use of DXA limits the ability to screen large populations for bone quality.

Ultrasonography (US) of the calcaneus has become an accepted method of evaluating bone quality to identify people at risk for osteoporosis. The benefits of US as a screening tool are ease of use, portability, and relative affordability of the machine. In addition, there is minimal, if any, risk to the patient. A variety of US machines are available, which has made it difficult to standardize data generated from US to the criterion standard data provided by DXA. Therefore, one aim of this study was to establish a range of output from US of the calcaneus that correlates to data from DXA scanning indicating good vs poor BMD.

Vitamin D is a primary player involved in bone metabolism. The importance of vitamin D to bone health is illustrated by its deficiency resulting in osteomalacia in adults and rickets in children. One of its critical roles is regulating calcium levels, which affect bone mineralization. Because it plays an important role in bone biology, clinical guidelines from various organizations support the assessment of and treatment with vitamin D in the management of bone health. Although its role in maintaining BMD and reducing the risk of fracture is arguable, we questioned whether assessing vitamin D levels in conjunction with BMD may provide a more rigorous screening tool to identify individuals at risk for low BMD.

The current study was designed to establish the validity of US as a screening tool to assess bone health and to determine whether measuring the circulating concentration of vitamin D improves the predictability of US to identify individuals at risk for having low BMD. Using US as a screening method will permit large populations to be assessed for bone quality with the hope that accessible early detection will enable interventions to occur before BMD is lost to a critical level. Ultrasonography’s lower cost, reduced technical needs, and low risk to patients facilitates the practice of preventive medicine in primary care settings.

Methods
This study was approved by the West Virginia School of Osteopathic Medicine Institutional Review Board. Participants were recruited between June 2015 and June 2016 from the Robert C. Byrd Clinic, a rural, primary care facility in Lewisburg, West Virginia. Patients aged 18 years or older scheduled for DXA were eligible for inclusion in the study. Patients wearing stockings that could not be removed were excluded from the study because stockings interfere with US. Research personnel obtained a weekly schedule of appointments for DXA scans and recruited individuals into the study at the beginning of their appointment. Data were not collected regarding patients who did not agree to participate. The clinic staff was aware of the study, but referring physicians were likely unaware of the project. Hence, the participants scheduled for DXA most likely reflected individuals who either met screening guidelines or whose BMD was
being analyzed for some other reason (eg, recent fracture, medications).

Informed written consent was obtained from all participants. Participants could agree to calcaneus US only, or calcaneus US and fingerstick blood testing in addition to the DXA scan. At the time of screening, participants also filled out a questionnaire. Information that was collected included some parameters associated with the Fracture Risk Assessment Tool (FRAX) calculation (age, sex, weight, height, previous fracture, parental hip fracture, current smoker, glucorticoid use, rheumatoid arthritis, 3 or more alcoholic drinks per day). The collected information also included the first day of last menstrual period for premenopausal women, calcium or vitamin D supplement use, and use of drugs that could affect BMD (eg, steroids, diuretics, anticoagulants, thyroid hormone, proton pump inhibitors).

An Achilles bone ultrasonometer (GE Healthcare) was used to assess the density of the calcaneus (Figure 1). The shoe and sock were removed from the right foot and the heel was sprayed with rubbing alcohol. The foot was then placed in the cradle of the US machine, and after recording the BMD T score and Z score readings, the foot was removed and dried, and the sock and shoe were donned. This procedure was then repeated with the left foot.

Blood was collected for vitamin D analysis using the standard sterile protocol for daily assessment of circulating concentrations of glucose. The blood was placed on a ZRT blood spot card and allowed to dry (Figure 2). Blood spot cards were stored at −80°C until analyzed for 25-hydroxyvitamin (25[OH]D) D₂ and D₃ by ZRT Laboratories using liquid chromatography–tandem mass spectrometry.¹¹ The intra-assay coefficient of variation for 25(OH)D D₂ and D₃ was 8.1% and 9.2%, respectively; the interassay coefficient of variation was 13% and 12%, respectively. The limit of sensitivity for 25(OH)D D₂ and D₃ was 0.5 and 1.9 ng/mL, respectively.

After US data were recorded and blood collected by research personnel, DXA was performed by trained technologists Lunar Prodigy Advance (GE Healthcare). The computed T and Z scores for the spine and left and right femurs were recorded by research personnel.

Data were analyzed using SAS software (SAS Institute). Criteria were established to define a criterion standard of poor vs good BMD: a DXA BMD T score of the spine less than −1.0 was defined as poor, and a DXA BMD T score greater than or equal to −1.0 was defined as good. This cut point reflects the current diagnostic guideline from the World Health Organization in which DXA BMD T scores of −1.0 and above are categorized as normal, and DXA BMD T scores between

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**Figure 1.** An Achilles bone ultrasonometer (GE Healthcare) was used to assess the density of the calcaneus. After the shoe and sock were removed, the foot was sprayed with rubbing alcohol and placed in the cradle of the ultrasonometer and the BMD T score and Z score readings were recorded.

**Figure 2.** Blood was collected for Vitamin D analysis using ZRT blood spot cards. Analysis was conducted by ZRT laboratories using liquid chromatography–tandem mass spectrometry.
−1.0 and −2.5, as osteopenia. Bone mineral density T scores higher (more negative) than −2.5 correspond to osteoporosis.

Descriptive statistics were calculated. Pearson correlation coefficients were calculated within and between the DXA and US measurements, between the DXA and vitamin D levels, and between the US measurements and vitamin D levels. The Wilcoxon signed rank test was used to compare the right vs left sides within the DXA and US measurements. A logistic regression model was fit using the new criterion standard as the outcome and the US measurements as explanatory variables. Area under the curve analysis using receiver operator characteristic curves was used to assess the predictive performance of the US readings on bone health as determined by DXA scan. Optimal cut points in the US readings, maximizing sensitivity and specificity, were determined for assigning poor vs good bone quality using our criterion standard. All tests were 2-sided, with significance level α=0.05 and P<0.05 considered statistically significant. The receiver operator characteristic curves were compared using the nonparametric approach of DeLong et al.

Results
Demographics of participants are presented in Table 1. Data were collected from 99 participants—13 men and 86 women. The median age of participants was 65 years (range, 27–94 years); mean BMI was 27.8. All participants were white, but data on ethnicity were not collected. Of the 99 individuals who agreed to participate in the study, 9 agreed only to US scanning. Therefore, analysis of vitamin D was conducted on 90 participants, and 4 of the samples fell below the limit of sensitivity. As defined by our criteria, 37 participants had poor BMD and 57 had good BMD. Data were missing from 5 individuals (not scanned owing to metal in spine).

For each participant, US recordings of a T score were obtained for both the left and right foot, and these values were compared with the T score from the participants’ DXA scan of their spine performed during the same visit. No statistically significant differences were found between US values from scans of the left vs the right foot (data not shown). Ultrasonography readings of either the left or right foot were predictive of good vs poor bone quality (Table 2; Figure 3). The area under the curve values for the left and right foot US BMD T scores were 0.69 and 0.68, respectively (Figure 3). The cut point was −1.30 for the US BMD T score of the left foot that predicts good vs poor bone quality as determined by DXA scan area under the curve analysis, and the cut point value was −1.05 for the right foot (Table 2; Figure 3); a value above either reading indicates good bone quality, and a value below indicates poor bone quality.

Twenty-eight percent (24 of 86) of the participants had circulating concentrations of vitamin D less than 30 ng/mL. The sample population showed no correlation between BMD as assessed by US or DXA and circulating concentrations of vitamin D. Among participants who reported not taking vitamin D supplements, weak negative correlations were observed between circulating concentrations of vitamin D with DXA BMD T scores from the spine (−0.49; P=0.02) and right hip (−0.43; P=0.04) and DXA BMD Z score from the spine (−0.46; P=0.03).

Discussion
The current study validated the use of US as a screening tool to assess bone health. The findings from this study also determined that measuring circulating concentration of vitamin D did not improve the predictability of US to identify individuals at risk for having low BMD. A lack of association between BMD and circulating concentrations of vitamin D as seen in this study is not unique. There are reports of an absence of association between BMD, as determined by DXA scan, and vitamin D levels in children, adults with primary hyperparathyroidism, obese adults, and Middle Eastern adults. The current findings could be due to the small sample size or bias of the sample population.
Since persons scheduled for DXA were invited to participate in the study, many may have already been identified to have poor BMD or had suspected poor BMD. Seventy-one of 99 participants (72%) reported taking vitamin D supplements, and 58 of 99 participants (59%) reported taking calcium supplements. It cannot be determined from the data how long they had been taking supplements and whether their use was compliant with physician or manufacturer recommendations.

Ad eciency in vitamin D is the cause of bone diseases such as rickets and osteomalacia. Therefore, the negative relationship seen in this study between BMD and circulating concentrations of vitamin D was not expected. Although a 2013 study\textsuperscript{16} reported a negative relationship between BMD and vitamin D supplementation, it was observed at only select skeletal sites in a relatively short study that also had a small sample size. A negative correlation was also reported between BMD and circulating concentrations of vitamin D in children.
with ulcerative colitis. More work is needed to clarify the association of circulating concentrations of vitamin D and BMD and how it may be influenced in select populations. As is true with many aspects of medicine, the function of bone is tightly correlated to its structure. When it comes to the compromised structure of bone that leads to osteoporosis, there are 2 primary risk factors:

### Table 2.
**Odds Ratio From Logistic Regression Analysis Determining Good vs Poor Bone Quality as Assessed by Ultrasonography (N=99)**

<table>
<thead>
<tr>
<th>Ultrasonography Reading</th>
<th>OR</th>
<th>CI</th>
<th>P Valuea</th>
<th>Cut Point</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>LT</td>
<td>0.537</td>
<td>0.34-0.84</td>
<td>.007</td>
<td>−1.30</td>
<td>0.63</td>
<td>0.63</td>
</tr>
<tr>
<td>LZ</td>
<td>0.596</td>
<td>0.40-0.89</td>
<td>.01</td>
<td>0.15</td>
<td>0.60</td>
<td>0.57</td>
</tr>
<tr>
<td>RT</td>
<td>0.600</td>
<td>0.40-0.90</td>
<td>.01</td>
<td>−1.05</td>
<td>0.65</td>
<td>0.65</td>
</tr>
<tr>
<td>RZ</td>
<td>0.643</td>
<td>0.44-0.94</td>
<td>.022</td>
<td>0.50</td>
<td>0.60</td>
<td>0.61</td>
</tr>
</tbody>
</table>

*a* P<.05 was considered significant.

**Abbreviations**: LT, T score from US of left calcaneus; LZ, Z score from US of left calcaneus; RT, T score from US of right calcaneus; RZ, Z score from US of right calcaneus.

![Figure 3.](image)

Area under curve analysis results from ultrasonography (US) of the left and right calcaneus. **Abbreviations**: LT, T score from US of left calcaneus; LZ, Z score from US of left calcaneus; RT, T score from US of right calcaneus; RZ, Z score from US of right calcaneus.
age and failure to accrue optimal BMD. As one ages, many factors contribute to unbalancing the bone remodeling cycle, for example, changes in circulating hormones such as estrogens, androgens, and parathyroid hormone. Effective amassing of bone is considered to occur between childhood and early adulthood. Peak BMD is attained by the mid to late 20s. Failure to attain peak BMD can be caused by poor nutrition, lifestyle, environmental stressors, lack of physical activity, or genetic makeup. Aside from the latter factor, all of the risks to establishing peak BMD are modifiable. In addition, hormonal therapies, lifestyle changes, and pharmacologic interventions can improve BMD in spite of the aging process. The critical factor in preventing osteoporotic fractures is to identify persons at risk for the disease and intervening early to obviate the loss of BMD. The current study established cut point US BMD T scores of the calcaneus as a low-cost, non-invasive, portable screening method to identify adults who may be at risk for osteoporosis.

One example of how assessing bone quality with US could improve screening for osteoporosis is in the field of men’s health. The risk of osteoporosis in men is an important medical concern that has been underappreciated. The risk of osteoporotic bone fracture in a man older than 50 years is 27% higher than his lifetime risk of prostate cancer developing. Also of concern is the fact that the mortality associated with hip and other fragility fractures is higher in men than in women. Screening men for osteoporosis is not recommended until the age of 70 years unless there are existing risks for low BMD, such as glucocorticoids or other medications known to affect BMD. However, by age 70, treatment would consist of primarily pharmacologic management. If at-risk persons can be identified earlier, lifestyle modifications can be implemented before BMD declines to problematic levels.

As mentioned above, one limitation of this study could be a bias in the sample population. Since patients were already scheduled for DXA when they were recruited into the study, they may have had indicators of poor bone quality. Such a bias may have affected the findings relating circulating concentration of vitamin D to DXA and US output, but it should not have influenced the correlation of DXA and US data. The maximum SD in the DXA and US measurements was less than 1.7. A difference of 1 unit in T or Z scores should have been detectable between 2 prognostic groups having a sample size of at least 46 participants each with a power of 80%.

Another limitation of the study is the homogeneous nature of the sample population. Ethnic background can influence expected BMD. Therefore, screening patients for good vs poor bone quality as we have defined in this manuscript is most appropriate for whites. The study population also comprised primarily older women. The software generating output from both DXA and US machines use the same standard curve (generated using data from young adult women); hence, the fact that our sample population comprised predominantly older women would not influence the outcome of the study.

Future studies should include screening young adults to determine whether there is proper deposition of bone during a time when lifestyle modifications could potentially improve BMD. Assessing youth and young adult populations in various geographical regions may also improve our understanding of how socioeconomic and educational status may affect bone quality and help to determine whether interventions might improve the deposition of bone to help stave off or decrease fracture risk due to fragility associated with aging.

Conclusion

Ultrasoundography provides a method to screen large numbers of people for bone health, as it is portable, relatively low cost, and confers no risk to patients. This study established a US BMD T score greater than 1.05 of the right heel as a potential indicator of good bone health, whereas a US BMD T score less than −1.05, poor bone health. The US BMD T score was chosen as the evaluator of bone health because the diagnosis of osteoporosis is determined by a DXA.
BMD T score and would therefore be recognized by physicians. In addition, the data collected indicate that measuring the circulating concentration of vitamin D does not improve the predictability of US to identify persons at risk for having low BMD.

**Author Contributions**

All authors provided substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; Drs Komar and Bauer drafted the article or revised it critically for important intellectual content; Drs Komar and Bauer gave final approval of the version of the article to be published; and all authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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**References**


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