

Interpretation of Calcaneus Dual-Energy X-Ray Absorptiometry Measurements in the Assessment of Osteopenia and Fracture Risk

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ABSTRACT

Dual-energy X-ray absorptiometry (DXA) of the calcaneus is useful in assessing bone mass and fracture risk at other skeletal sites. However, DXA yields an areal bone mineral density (BMD) that depends on both bone apparent density and bone size, potentially complicating interpretation of the DXA results. Information that is more complete may be obtained from DXA exams by using a volumetric density in addition to BMD in clinical applications. In this paper, we develop a simple methodology for determining a volumetric bone mineral apparent density (BMAD) of the calcaneus. For the whole calcaneus, $BMAD = (BMC)/A_{DXA}^{3/2}$, where BMC and A_{DXA} are, respectively, the bone mineral content and projected area measured by DXA. We found that $A_{DXA}^{3/2}$ was proportional to the calcaneus volume with a proportionality constant of 1.82 ± 0.02 (mean \pm SE). Consequently, consistent with theoretical predictions, BMAD was proportional to the true volumetric apparent density (ρ) of the bone according to the relationship $\rho = 1.82$ BMAD. Also consistent with theoretical predictions, we found that BMD varied in proportion to $\rho V^{1/3}$, where V is the bone volume. We propose that the volumetric apparent density, estimated at the calcaneus, provides additional information that may aid in the diagnosis of osteopenia. Areal BMD or BMD^2 may allow estimation of the load required to fracture a bone. Fracture risk depends on the loading applied to a bone in relation to the bone's failure load. When DXA is used to assess osteopenia and fracture risk in patients, it may be useful to recognize the separate and combined effects of applied loading, bone apparent density, and bone size. (J Bone Miner Res 2000;15:1573–1578)

Key words: osteopenia, fracture risk, bone mineral density, bone mineral apparent density, apparent density

INTRODUCTION

THE CALCANEUS has shown promise as a site for measuring bone density and predicting fracture risk. Calcaneal bone mineral density (BMD) correlates with the BMD of other skeletal sites including the lumbar spine^(1,2) and the proximal femur.^(3,4) Calcaneal BMD and bone mineral content (BMC) are also good predictors of fracture risk.^(1,3,5–7) Black et al.⁽⁶⁾ found that calcaneal BMD predicts the occurrence of nonspine fractures at least as well as BMD of the proximal femur, lumbar spine, proximal radius, and

distal radius. Similarly, Wasnich et al.⁽⁵⁾ found calcaneal BMC to be better than BMC of the lumbar spine, proximal radius, and distal radius in predicting overall fracture incidence for all skeletal sites. Not only is BMD of the calcaneus a good predictor of overall fracture risk, it can predict fracture risk at specific sites almost as well as, and sometimes better than, BMD measured at the potential fracture site.^(1–3,6,7)

Several densitometry techniques have been used on the calcaneus including single- and dual-photon absorptiometry (SPA and DPA, respectively), single- and dual-energy

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X-ray absorptiometry (SXA and DXA, respectively), quantitative computed tomography (QCT), and quantitative ultrasound (QUS). This study focuses on DXA, an established technique that is widely used clinically. Although DXA has many advantages including high precision and low radiation exposure, it measures an areal BMD rather than a true volumetric density. This may complicate the interpretation of DXA results because low BMD may result from low volumetric density, small bone size, or a combination of the two.

To try to improve the interpretation of DXA measurements, one must understand the difference between geometric, material, and structural properties. Geometric properties describe the size and shape of a structure. Material properties describe the substance out of which a structure is made. Geometric and material properties are independent of each other. Structural properties take into account both geometry and material.

DXA normally gives a BMC measured in grams, a projected area (A_p) measured in centimeters squared, and an areal BMD ($BMD = BMC/A_p$) measured in grams per centimeter squared. The areal BMD is a structural property that depends on both the volumetric apparent density of the bony tissue and the size of the bone. When interpreting DXA measurements, it may sometimes be useful to separate the effects of apparent density and size. This can be accomplished by determining a volumetric density that eliminates the effects of bone size.

Carter et al.⁽⁸⁾ introduced a general approach for calculating a volumetric bone mineral apparent density (BMAD) based on densitometric measurements. In their approach, Carter et al. assumed that a measure t^* could be identified that was proportional to the average thickness (t_{ave}) of the bone in the region scanned. The total volume of the scanned bone including both marrow spaces and bony tissue is $V = A_p t_{ave}$. This volume is proportional to a reference volume $V^* = A_p t^*$ because $t^* \propto t_{ave}$. The BMAD was defined as $BMAD = BMC/V^* = BMC/(A_p t^*)$. This measure is proportional to the true volumetric apparent density of the structure, which is defined as $\rho = BMC/V$.

To illustrate these relationships, consider a homogeneous cube of bone with volume V and volumetric apparent density ρ . The cube has projected area $A_p = V^{2/3}$ and thickness $t = V^{1/3}$. In this case, the reference thickness is assumed to be equal to the known thickness of the specimen so that $t^* = t$. The $BMC = \rho V$. The areal $BMD = BMC/A_p$, and the $BMAD = BMC/(A_p t^*)$. The volumetric BMAD therefore is proportional to ρ and independent of V whereas the areal density (BMD) varies in proportion to $\rho V^{1/3}$ (Fig. 1).

In this paper, we develop a method for calculating BMAD of the calcaneus by identifying an appropriate reference thickness t^* using standard noninvasive clinical measures. We also determine an equation for calculating the apparent density ρ once BMAD is known. Finally, we discuss the use of BMD, BMAD, and ρ in clinical applications such as the diagnosis of osteopenia and the assessment of fracture risk.

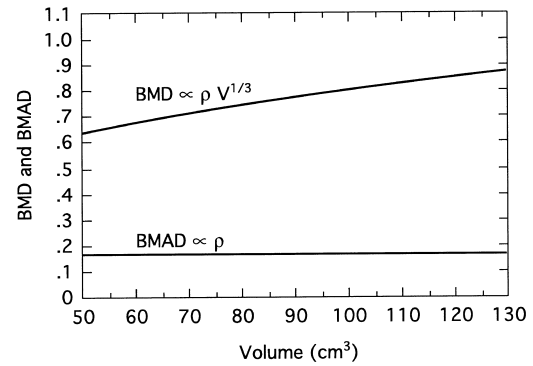


FIG. 1. Theoretical dependence of BMD and BMAD on specimen volume for a homogeneous cube of bone.

MATERIALS AND METHODS

For this study, we used 23 fresh frozen calcanei from 13 human cadavers aged 35–68 years (mean \pm SD; 56.2 ± 9.2 years). We first determined the volume of each calcaneus using a water displacement method. After determining the weight (W_1) of a beaker full of water, we allowed the calcaneus to displace water from the beaker and determined the weight of the beaker and remaining water (W_2). Because the density of water is 1 g/mm^3 , the calcaneus volume (V_{disp}) in millimeters cubed is equal to the weight of the displaced water ($W_1 - W_2$) in grams. This method of measuring volume was determined to be accurate to within 4% for five repeated measurements of an aluminum block with dimensions similar to the calcaneus ($3 \times 4 \times 8 \text{ cm}$).

Next, we used calipers (CD-6'' CS, Mitutoyo Corp., Takatsu-Ku, Kawasaki-Shi, Japan) to measure the thickness of each specimen in the medial-lateral direction. We recorded one thickness measurement for each third of the posterior half of the calcaneus and one measurement for the anterior half. We used these measurements to estimate an average thickness for the bone (t_{calip}).

We then immersed each specimen in 15 cm of water and scanned the whole calcaneus using the fast spine protocol on a QDR-4000 bone densitometer with Hologic scanner software version V9.5 Rev A (Hologic, Waltham, MA, U.S.A.). For these scans, the X-ray beam was aligned in the medial-lateral direction. The densitometer provided BMC, projected area (A_{DXA}), and areal BMD measurements, where $BMD = BMC/A_{DXA}$. We calculated the volumetric bone apparent density as $\rho = BMC/V_{disp}$.

Because direct measurements of bone volume are not available for in vivo studies, an alternative methodology for computing the calcaneus volume is needed. One approach is to calculate the volume of the calcaneus by multiplying the projected area given by DXA with the average thickness of the calcaneus. The problem of determining calcaneus volume therefore reduces to the problem of estimating the average thickness of the calcaneus. We measured the thickness earlier using calipers, and we also can calculate the thickness as $t_{disp} = V_{disp}/A_{DXA}$. We used linear regression to

TABLE 1. SLOPES OF LINEAR REGRESSIONS FOR CALCANEUS THICKNESS VERSUS SCALING VARIABLES ASSUMING GEOMETRIC SIMILARITY

Variable	Measurement technique	r ²	p value
(Subject weight) ^{1/3}	Caliper	0.15	0.0653
	Displacement	0.08	0.1816
(Subject height) ¹	Caliper	0.55	<0.0001
	Displacement	0.34	0.0038
(Calcaneus area) ^{1/2}	Caliper	0.65	<0.0001
	Displacement	0.44	0.0006

compare these two methods of determining the calcaneus thickness.

The above thickness measurements, obtained using invasive techniques, were used to develop a simple noninvasive method for estimating the average thickness of the calcaneus. This method employed scaling techniques as described by Carter et al.⁽⁸⁾ Geometric similarity dictates that areas are proportional to lengths squared, volumes are proportional to lengths cubed, and weights are proportional to volumes. Under geometric similarity, the calcaneus thickness therefore would be proportional to (subject weight)^{1/3}, (subject height)¹, and (calcaneus area)^{1/2}. We performed linear regressions of the measured calcaneus thicknesses (*t*_{calip} and *t*_{disp}) versus these variables to see which one represented geometric similarity the best. The scaling variable giving the highest *r*² and lowest *p* values was selected as the thickness measure *t*^{*}.

Having identified a measure *t*^{*}, which is proportional to the measured calcaneus thickness, we calculated the BMAD as BMAD = BMC/*V*^{*} = BMC/(*A*_{DXA}*t*^{*}). We performed simple linear regressions of BMD and BMAD versus calcaneus volume to investigate the dependence of BMD and BMAD on calcaneus size. To compare the experimental results for BMD with the theoretical prediction shown in Fig. 1, we determined exponent values for the power relationship BMD ∝ ρ^{*x*} (*V*_{disp})^{*y*} using a multiple regression of log(BMD) versus log(ρ) and log(*V*_{disp}). We also used simple linear regression to examine the relationship between *V*^{*} and *V*_{disp}. The results of this regression were used to evaluate the relationship ρ = *k* BMAD because BMAD = BMC/*V*^{*} and ρ = BMC/*V*_{disp}. Where appropriate, data are reported as mean ± SE. A value of *p* < 0.05 is considered statistically significant.

RESULTS

We obtained similar thickness values for the calcaneus using the caliper and water displacement methods. Linear regression comparing the two methods gave the relationship *t*_{disp} = 0.986 *t*_{calip} (*r*² = 0.72; *p* < 0.0001). We conclude that either method may be used to determine the average thickness of excised calcanei.

The linear regressions of both *t*_{calip} and *t*_{disp} versus the geometrically scaled variables showed that (subject

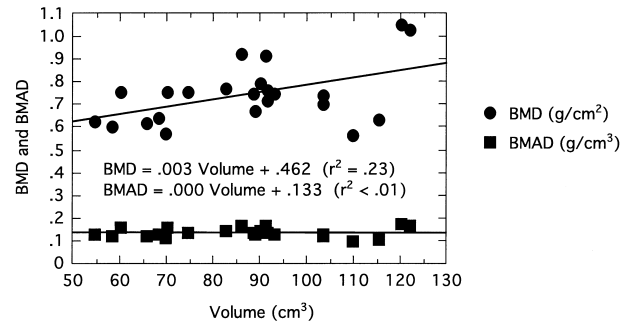


FIG. 2. Linear regressions of BMD and BMAD versus calcaneus volume. The results show that BMD increases with calcaneus size whereas BMAD is independent of calcaneus size.

weight)^{1/3} was the only poor predictor of calcaneus thickness with low *r*² and high *p* values (Table 1). The variable (calcaneus area)^{1/2} predicted calcaneus thickness slightly better than (subject height)¹ with higher *r*² values and lower *p* values. We therefore selected (calcaneus area)^{1/2} as the measure *t*^{*} used to estimate calcaneus thickness. Given *t*^{*} = *A*_{DXA}^{1/2} and *V*^{*} = *A*_{DXA} *t*^{*} = *A*_{DXA}^{3/2}, we calculated the BMAD as BMAD = BMC/*V*^{*} = BMC/*A*_{DXA}^{3/2}.

Linear regressions of BMD and BMAD versus calcaneus volume showed that BMAD is independent of bone volume (slope = 6.3E-5 ± 2.3E-4) whereas BMD increases with increasing bone volume (slope = 0.003 ± 0.001; Fig. 2). The slope of BMAD versus *V*_{disp} was not significantly different from zero (*p* = 0.79), whereas the slope of BMD versus *V*_{disp} was significantly different from zero (*p* < 0.05). As expected, BMAD eliminated the effects of bone size.

These results are consistent with the theoretical predictions shown in Fig. 1. The multiple regression gave *x* = 0.888 ± 0.057 and *y* = 0.347 ± 0.040 for the power law BMD ∝ ρ^{*x*} (*V*_{disp})^{*y*}. The theoretical prediction is BMD ∝ ρ^{1.0} (*V*_{disp})^{1/3} (Fig. 1). The exponents predicted by theory fall within the 95% confidence intervals determined by the multiple regression (0.769–1.008 for *x*; 0.263–0.431 for *y*).

Linear regression of *A*_{DXA}^{3/2} versus *V*_{disp} indicated a significant linear relationship between the two variables with *p* < 0.0001 and *r*² = 0.92. The constant of proportionality for this relationship is *k* = 1.82 ± 0.02. The linear relationship verifies that ρ is proportional to BMAD because ρ = BMC/*V*_{disp} and BMAD = BMC/*A*_{DXA}^{3/2} yielding the additional relationship ρ = 1.82 BMAD (Fig. 3).

DISCUSSION

In this paper, we have developed a simple methodology for determining the volumetric apparent density of the calcaneus given standard DXA measurements. We showed that the calcaneus scales according to geometric similarity with the average thickness of the calcaneus being proportional to *t*^{*} = *A*_{DXA}^{1/2}. This relationship allows calculation of the volumetric BMAD as BMAD = BMC/*A*_{DXA}^{3/2}. The volumetric apparent density (ρ) is proportional to BMAD with

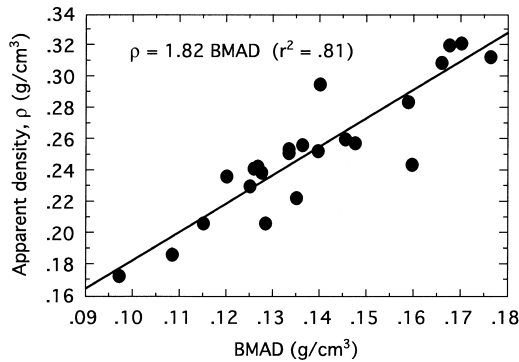


FIG. 3. Linear relationship between ρ and BMAD.

proportionality constant $k = 1.82 \pm 0.02$. Apparent density therefore can be estimated as $\rho = 1.82 \text{ BMAD}$. By considering BMAD and ρ in addition to BMD, we may be able to improve the utility of DXA measurements in clinical applications.

For example, osteopenia is a condition characterized by low bone density in comparison with controls. Osteopenia currently is assessed using BMD values. Consequently, large individuals with low volumetric bone density are not diagnosed as osteopenic if they have normal BMD because of large bone size. Conversely, small individuals with high volumetric bone density are characterized as osteopenic if they have low BMD because of small bone size. By examining BMAD or ρ in addition to BMD, the physician would be able to distinguish between patients with similar BMD values but different volumetric bone densities. This additional information could aid the physician in determining appropriate treatment options for individual patients.

The load required to fracture a bone is a structural property that depends on both apparent density and bone size. Because BMD includes both density and size effects, it turns out that BMD is a useful predictor of whole bone strength.⁽⁹⁾ The failure load of a whole bone should be proportional to BMD^2 (see Appendix for explanation). When BMD is used to predict whole bone strength, BMD^2 therefore should be considered instead of, or in addition to, BMD. Because structural strength varies as BMD^2 , a decrease in BMD to 50% of normal implies a decrease in failure load to 25% of normal. If only BMD were examined, the failure load would be overestimated. Therefore, it may be important to consider BMD^2 as well as BMD when assessing the failure load of a bony structure.

Failure load is a useful measure of whole bone strength, but it does not necessarily reflect fracture risk. The risk of fracturing a bone depends on the loading applied to the bone in relation to the bone's failure load. For example, small individuals with normal volumetric bone density may have low BMD and low whole bone failure loads, but they should generate correspondingly low loads during normal activities of daily living and during falls. Because low failure loads are offset by low applied loading, fracture risk should not be increased in these individuals despite their low BMD. Both applied loading and failure loads should be considered when assessing fracture risk.

A possible index for fracture risk assessment is $\text{Risk}_{\text{fx}} = F_{\text{applied}}/F_{\text{fail}} \propto \text{BW}/\text{BMD}^2$, where BW represents body weight. Higher values of the index indicate higher fracture risk. BW is used as a first approximation of the applied loads because heavier individuals tend to generate larger loads during activities of daily living and during falls. Low BMD caused by small bone size normally will be balanced by low BW. However, low BMD caused by low apparent density will not be balanced by BW and will result in increased fracture risk. This method of assessing fracture risk is consistent with other studies that have identified bone density and applied loading as the main determinants of fracture risk.⁽¹⁰⁾ Other factors such as bone geometry, trabecular architecture, and propensity to fall also affect fracture risk.^(10,11) Our fracture risk index does not account for these additional variables.

As an alternative to correcting for size by calculating BMAD and ρ , the standards against which BMD measurements are compared could be further adjusted for size. Currently, Hologic provides reference data from sex-matched young normals for the calculation of T scores and reference data from sex- and age-matched controls for the determination of Z scores.⁽¹²⁾ Reference data reflecting additional size differences also would be useful. BMD already includes some size adjustment by factoring in projected area. The remaining size bias can be removed by accounting for bone thickness. Because the calcaneus thickness scales geometrically with respect to subject height but not weight (Table 1), reference data grouped by patient height might be most useful.

The relationships presented in this paper apply to DXA measurements performed on the calcaneus. Many studies have shown that the calcaneus is a good site for assessing bone density and fracture risk.⁽¹⁻⁶⁾ With more careful interpretation of the DXA results using BMAD and ρ in addition to BMD, it may be possible to establish even better relationships between properties of the calcaneus and properties of other sites such as the hip and spine. Because individuals with large calcanei are likely to have correspondingly large femurs and vertebrae, fracture risk assessed using Risk_{fx} of the calcaneus is likely to reflect fracture risk at the hip and spine. In cases of osteoporosis, decreased apparent density is expected at multiple sites including the calcaneus, hip, and spine.^(2,13) BMAD and ρ of the calcaneus therefore should be useful in diagnosing osteopenia of the hip and spine.

The relationships derived in this study are specific to the region examined, namely, the whole calcaneus. If other regions are examined, new equations for calculating BMAD and ρ must be formulated. Similar relationships ($\text{BMAD} = \text{BMC}/A_{\text{DXA}}^{3/2}$) have been used for BMAD of vertebral bodies^(8,14-16) while other relationships have been used for BMAD of other sites including the radius, femoral neck, and whole body.^(14,17,18) However, even when the same relationship is used BMAD is specific to a particular region because of differences in bone geometry between different locations. For example, BMAD of the posterior half of the calcaneus differs from BMAD of the whole calcaneus and BMAD of the L2 vertebral body even if $\text{BMC}/A_{\text{DXA}}^{3/2}$ is used in all cases. However, once the apparent density ρ is

determined, it can be compared across sites. If density measurements are always taken for the whole calcaneus, BMAD and ρ are both appropriate parameters for examination. However, if density measurements are taken at different axial and appendicular sites, only ρ should be used.

BMAD and ρ offer the theoretical advantage of separating volumetric bone density from effects caused by bone size. Although previous studies have not shown BMAD

to be a better general predictor of fracture risk than BMD,^(17,18) the theoretical advantages of BMAD and ρ suggest that they may be particularly useful in some situations. BMAD and ρ should be most useful when large size differences exist such as in pediatrics and in cases involving very small or very large adults. The use of BMAD and ρ in these clinical settings warrants further investigation.

In summary, we have presented a methodology for calculating BMAD and ρ of the calcaneus based on standard DXA measurements. These volumetric densities eliminate the effects of bone size inherent in BMD, allowing more accurate assessment of material properties and possibly better diagnosis of osteopenia. BMD is useful for predicting the load at which a bone will fracture, but applied loading also should be taken into account to assess fracture risk. By considering the material properties BMAD and ρ in addition to the structural property BMD, we may be able to better interpret DXA measurements in clinical applications.

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APPENDIX

Carter and Hayes⁽¹⁹⁾ showed that the material strength (σ_{fail}) of human bone specimens is approximately proportional to the volumetric apparent density squared (ρ^2). The force required to fracture a bone is therefore $F_{\text{fail}} = \sigma_{\text{fail}} A \propto \rho^2 A$, where A is the cross-sectional area of the bone. The areal BMD measured by DXA is proportional to $(\rho^2 A)^{1/2}$ as noted by Carter et al.⁽⁹⁾ Therefore, $\text{BMD}^2 \propto \rho^2 A$ and $F_{\text{fail}} \propto \text{BMD}^2$. The load required to fracture a whole bone thus should be proportional to BMD^2 .

Previous studies have shown significant linear correlations between whole bone failure loads and BMD.^(3,20,21) However, these studies have not examined the relationship between failure load and BMD^2 . In addition, regressions are often performed between failure load and BMD without forcing the regression line through the origin. Because the failure load theoretically should be zero when BMD is zero, it is reasonable to look at regressions of failure load versus BMD or BMD^2 that pass through the origin.

In this Appendix, we reanalyze data from Bouxsein et al.⁽³⁾ to illustrate the relationships between whole bone failure load, BMD, and BMD^2 . Bouxsein et al. previously showed a strong linear correlation between femoral failure load and femoral neck BMD (Fig. 4A, dashed line). However, as previously discussed, the regression theoretically should pass through the origin (Fig. 4A, solid line). Forcing the regression through the origin reduces the r^2 value from 0.79 to 0.75. A better regression is obtained using BMD^2 instead of BMD, again forcing the regression line through the origin (Fig. 4B). In this case, the r^2 value increases to 0.82.

Because of the relatively small number of data points available, there are no statistically significant differences between the three regressions in Fig. 4. However, theoretical considerations dictate that the whole bone failure load should be proportional to BMD^2 with a failure load of zero when BMD is zero. This relationship gave the highest r^2 value for the data examined (Fig. 4).

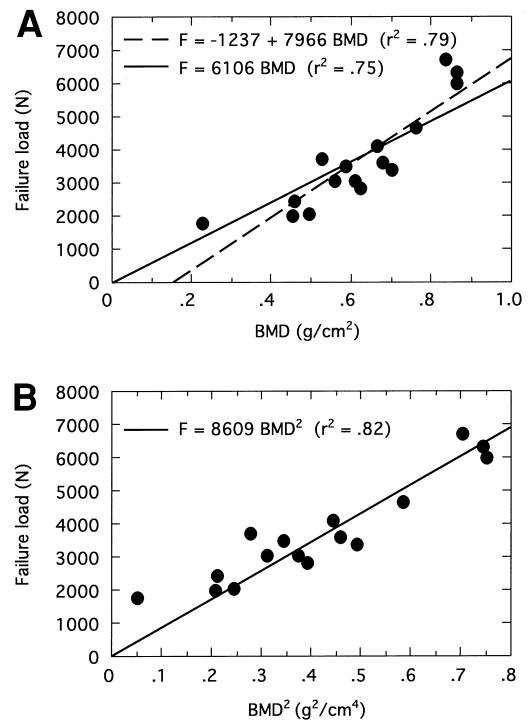


FIG. 4. Linear regressions of femoral failure load versus (A) femoral neck BMD and (B) femoral neck BMD squared. The data shown is from Bouxsein et al.⁽³⁾ The solid lines indicate regressions forced through the origin. The dashed line represents the regression presented by Bouxsein et al.⁽³⁾