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The Influence of Bone Volume Fraction and Ash Fraction on Bone Strength and Modulus

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Although bone strength and modulus are known to be influenced by both volume fraction and mineral content (ash fraction), the relative influence of these two parameters remains unknown. Single-parameter power law functions are used widely to relate bone volume or ash fraction to bone strength and elastic modulus. In this study we evaluate the potential for predicting bone mechanical properties with two-parameter power law functions of bone volume fraction (BV/TV) and ash fraction (α) of the form $y = a(\mathrm{BV/TV})^b\,\alpha^c$ (where *y* is either ultimate strength or elastic modulus). We derived an expression for bone volume fraction as a function of apparent density and ash fraction to perform a new analysis of data presented by Keller in 1994. Exponents *b* and *c* for the prediction of bone strength were found to be 1.92 ± 0.02 and 2.79 ± 0.09 (mean ± SE), respectively, with $r^2 = 0.97$. The value of *b* was found to be consistent with that found previously, whereas the value of *c* was lower than values previously reported. For the prediction of elastic modulus we found *b* and *c* to be 2.58 ± 0.02 and 2.74 ± 0.13, respectively, with $r^2 = 0.97$. The exponent related to ash fraction was typically larger than that associated with bone volume fraction, suggesting that a change in mineral content will, in general, generate a larger change in bone strength and stiffness than a similar change in bone volume fraction. These findings are important for interpreting the results of antiresorptive drug treatments that can cause changes in both ash and bone volume fraction. (Bone 29:74–78; 2001)
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Introduction

Bone volume fraction (BV/TV; bone volume/bulk volume) and ash fraction (α; ash mass/dry bone mass) each have a significant influence on the mechanical properties of bone.[4,23] The relative influence of these parameters, however, is not well known. Ash fraction, in particular, is rarely presented in studies, but has recently received increased attention in the literature. Variations in ash fraction can be caused by bone diseases[17] (osteomalacia, Paget's disease) or treatment with certain antiresorptive drugs[1,3] (bisphosphonates). Meunier and Boivin[16] recently indicated that variation in ash fraction may explain how small increases in areal bone mineral density (BMD; measured by dual-energy X-ray absorptiometry) are correlated with unexpectedly large decreases in fracture incidence in patients taking bisphosphonates. Further understanding of the relative influences of ash fraction and bone volume fraction on bone mechanical properties could help in evaluating this possibility.

Mechanical testing of bone samples has identified the apparent density (mineralized bone mass/bulk volume) and the ash apparent density (ash mass/bulk volume) as effective predictors of bone strength and stiffness.[15] These parameters are used to predict bone material properties with power law functions of the form[2]:

$$y = a\,x^b \tag{1}$$

where *y* is the strength or elastic modulus, *x* is a parameter value (e.g., apparent density or ash apparent density), and *a* and *b* are empirical constants derived from experimental data. Bone volume and ash fraction influence both apparent density and ash apparent density. One limitation of models based on apparent density or ash apparent density is that they do not separate the influence of bone volume fraction from that of ash fraction. Single-parameter power law models using bone volume fraction or ash fraction can predict bone mechanical properties, but they are typically not as effective predictors as apparent density or ash apparent density.[15] This suggests that a power law model using both bone volume fraction and ash fraction could be effective at predicting bone mechanical properties while separating the influence of the two parameters.

Currey[6] has suggested a two-parameter power law function to differentiate the influences of bone volume and ash fraction on the elastic modulus of cortical bone. Currey's model used two independent parameters, bone volume fraction and calcium content (milligrams calcium per gram total). Currey found that this model explained >80% of the variance in the data from a sample set that included bone from 18 different species with a wide range in ash fraction. Because elastic modulus is closely correlated with bone strength,[8] it is likely that the same mathematical form used to predict strength can also predict modulus. We therefore suggest predictive laws of the following form:

$$y = a\,(\mathrm{BV/TV})^b\,\alpha^c \tag{2}$$

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where *a*, *b*, and *c* are constants, and BV/TV is the bone volume fraction, α is the ash fraction, and *y* is either ultimate strength or elastic modulus.

The objective of this work is to determine the relative influences of bone volume fraction and ash fraction on the ultimate strength and elastic modulus of cancellous and cortical human bone with a large variation in ash fraction. Specifically, this involves analyzing or determining the values of *b* and *c* (see equation 2) that have been found in previous studies. Because there are few studies that have reported both bone volume fraction and ash fraction we derive an equation to determine the bone volume fraction given ash fraction and apparent density. This allows us to include data from a previous study that did not report bone volume fraction directly but did measure mechanical properties for a wide range of ash and apparent density.[12] The values of the exponents associated with bone volume fraction and ash fraction are used to assess the relative importance of these two parameters in determining bone material properties.

Methods

The specimens tested by Keller[12] showed a range in dry apparent density of 0.048 g/cm^3 (cancellous bone) to 1.885g/cm^3 (cortical bone), and a range in ash fraction from 0.174 to 0.662. Because Keller's data span such wide ranges in dry apparent density and ash fraction they are well suited to a two-parameter power law model (equation 2). Because bone volume fraction was not measured directly in Keller's study we derive an expression for the bone volume fraction in terms of parameters that were measured (apparent density and ash fraction). The apparent density, ρ, can be expressed as:

$$\rho = (\mathrm{BV/TV})\rho_t \quad (3)$$

where BV/TV is the bone volume fraction and ρ_t is the true tissue density of the bone.[14] By rearranging Equation 3, we express the bone volume fraction as:

$$\mathrm{BV/TV} = \frac{\rho}{\rho_t} \quad (4)$$

We now use the underlying constituents of bone tissue to derive an expression for the true tissue density, ρ_t, as a function of the ash fraction, α.

The ash fraction of osteoid ($\alpha = 0$) and fully mineralized bone ($\alpha = 0.70$) spans most ash fraction values observed in human bone. The dry tissue densities corresponding to these ash fraction values are 1.41 g/cm^3 and 2.31 g/cm^3 respectively.[14,20,21] Following Martin,[14] we use these points (0, 1.41 g/cm^3 and 0.7, 2.31 g/cm^3) to approximate the true tissue density, with a linear relationship between ash fraction and tissue density:

$$\rho_t\ (\mathrm{g/cm^3}) \approx 1.41 + 1.29\alpha \quad (5)$$

Using Equations 4 and 5 we obtain an expression for the bone volume fraction as a function of dry apparent density and ash fraction:

$$\mathrm{BV/TV} \approx \frac{\rho}{1.41 + 1.29\alpha} \quad (6)$$

Equation (6) is applied to Keller's original data to determine the bone volume fraction for each specimen tested. To validate this method, a comparison is made between the bone volume fraction predicted by Equation 6 and that derived from two-dimensional area fraction measurements obtained from a subset of Keller's data.[22] Bone area fraction is numerically equivalent to bone volume fraction.[18] The distribution of both bone volume and ash fraction is then quantitatively described.

The two-parameter power law model is achieved by linearizing Equation 2 using a logarithmic transform as follows:

$$\log(y) = \log(a) + b \log(\mathrm{BV/TV}) + c \log(\alpha) \quad (7)$$

Two-parameter multiple linear regression analyses were performed with EXCEL (Microsoft Corp., Redmond, WA) to determine the constants in Equation 7. The strength of the power law regressions was determined by analysis of the coefficient of determination (r^2) and the percent deviation from the model (PD) as shown by Keller.[12] A review of studies having reported ash fraction was also performed to determine the approximate range of values of model exponents indicated in the literature.

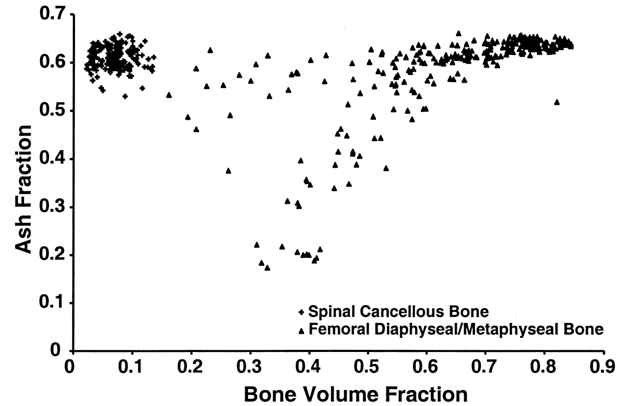

Figure 1. Distribution of bone volume and ash fraction. Samples marked with crosses are taken from the lumbar spine, and those marked with triangles are taken from the femur. The distribution in bone volume fraction and ash fraction is larger than that in previous studies (see Table 1). Bone volume fraction and ash fraction are poorly correlated (r^2 = 0.01), suggesting the two are independent parameters.

Results

Keller's data showed large variations in both bone volume and ash fraction (**Figure 1**). The equation derived for bone volume fraction (Equation 6) was a good predictor ($r^2 = 0.67$) of the bone volume fraction calculated from area fraction measurements in a subset of Keller's data (**Figure 2**). Bone volume fraction and ash fraction were found to be poorly correlated ($r^2 = 0.01$). The two-parameter best-fit power law models for Keller's data were found to be:

$$\log(\sigma_{\mathrm{ULT}}) = 794.33 + (1.92 \pm 0.02) \times \log(\mathrm{BV/TV}) + (2.79 \pm 0.09) \times \log(\alpha)\ r^2 = 0.97 \quad (8)$$

$$\log(E) = 84.37 + (2.58 \pm 0.02) \log(\mathrm{BV/TV}) + (2.74 \pm 0.13) \log(\alpha)\ r^2 = 0.97 \quad (9)$$

where σ_{ULT} is the compressive ultimate strength (MPa) and *E* is the elastic modulus (GPa), and the exponents are given as mean ± SE. Transformed back to original coordinates these equations are:

$$\sigma_{\mathrm{ULT}} = 794.33\ (\mathrm{BV/TV})^{1.92 \pm 0.02}\ \alpha^{2.79 \pm 0.09} \quad (10)$$

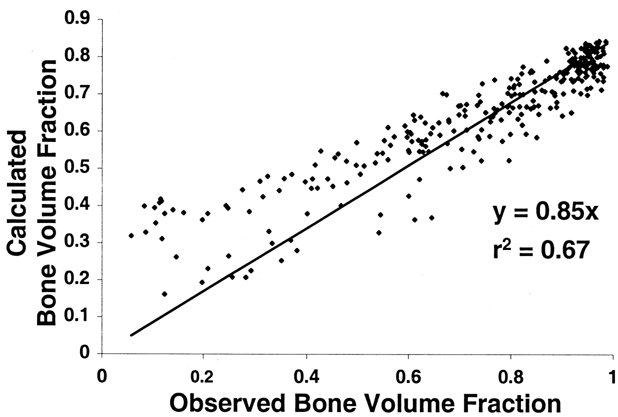

Figure 2. Bone volume fraction calculated using equation 6 is compared with that calculated from area fraction measurements taken from a subset of Keller's data.[12] The strong correlation ($r^2 = 0.67$) suggests that equation 6 is a good predictor of bone volume fraction for Keller's data.

$$E = 84.37\ (\mathrm{BV/TV})^{2.58 \pm 0.02}\ \alpha^{2.74 \pm 0.13} \tag{11}$$

The percent deviation rates for these two models are 29.7% (strength) and 43.4% (elastic modulus). A summary of the results from a reanalysis of Keller's data is given in **Table 1** along with a summary of previous studies that have correlated ash fraction with either strength or elastic modulus.

Discussion

The primary objective of this work was to evaluate the relative influence of volume and ash fraction on bone strength and elastic modulus over a broad range of volume and ash fraction values. The exponent values related to ash fraction were in both cases larger than those related to bone volume fraction. This suggests that a change in the ash fraction will generate a greater (and possibly much greater) change in bone strength and modulus than an identical change in bone volume fraction. The functions derived here (Equations 8 and 9) contributed to this analysis as they were developed from data with more variation in ash and bone volume fraction than previous studies (see Table 1), a condition known to improve the strength of statistical model.[13,19] The new two-parameter functions explain more of the variance in the data than single-parameter functions using either ash fraction or bone volume fraction (**Figure 3**).

Previous studies have used a number of loading conditions as well as samples from multiple species and different ranges of bone volume and ash fraction (Table 1). Power law models based on bone volume fraction or apparent density are comparable due to the direct relationship between the two parameters (Equation 3). The model for the prediction of bone strength showed an exponent value for bone volume fraction (1.92 ± 0.02) that was consistent with other studies analyzed (Table 1). A particularly large range of values for the ash fraction exponent was found in the literature (2.79–10.27). This range may be due, in part, to differences in loading conditions in the studies (tensile, compressive and bending) and is also influenced by the variation in bone volume and ash fraction between studies. With the exception of the current study, the only studies that have reported the ash fraction exponent used single-parameter power law models for the prediction of cortical bone strength.[7,24] The current study is different in that it used a two-parameter model to describe the strength of both cortical and cancellous bone. To better compare the current study with the previous studies we created a single-parameter power law model using a cortical bone subset of Keller's data (where bone volume fraction $>$0.60). The resulting ash fraction exponent value was larger than that found with all of Keller's data (3.54 instead of 2.79). It is possible that the ash fraction exponents in the other studies (7.70 and 10.27) are also slightly larger than they would have been if generated using both cortical and cancellous bone or data sets that had a larger range of ash fraction values. This is in agreement with previous observations that the range of the independent parameters used to develop a power law model can significantly influence the values of the exponents.[5,19] The current data, however, prevent us from making further conclusions regarding the value of the ash fraction exponent.

The model for the prediction of elastic modulus had an ash fraction exponent (2.74 ± 0.13) that was well within the range of values found by other studies (from 2.55 to 4.80). The bone volume fraction exponent (2.58 ± 0.02) was also within the

Table 1. Power law constants (exponents) for bone volume fraction (BV/TV) and ash fraction (α) are presented for this study and for other studies

				Strength exponent		Modulus exponent	
Source	Loading condition	α range	BV/TV range	BV/TV	α	BV/TV	α
Carter and Hayes,[2] Gibson[9]	Compression; human	NR	NR (cortical and cancellous)	2.0[a]	NR	2.0–3.0[a]	NR
Current study[12]	Compression; human	0.174–0.662	0.022–0.843 (cortical and cancellous)	1.92 (0.02)	2.79 (0.093)	2.58 (0.022)	2.74 (0.129)
Currey[7]	Tension; bovine	0.603–0.678	NR (cortical)	NR	7.7[b]	NR	4.8[b]
Currey[6]	Tension; Mammal, birds, reptiles	NR[c]	NR (cortical)	NR	NR	3.52	3.17[c]
Schaffler and Burr[23]	Tension; bovine	0.664–0.723	0.922–0.971 (cortical)	NR	NR	10.92[b] (1.64)	3.91[b] (1.11)
Vose and Kubala[24]	Bending; human	0.633–0.709	NR (cortical)	NR	10.27[b] (0.652)	NR	NR
Currey[6]	Bending; mammal; birds, reptile	NR[c]	NR (cortical)	NR	NR	3.13	2.55[c]

When available the standard error is reported in parentheses. The model citing the work of Vose and Kubala[24] was generated from a digitized plot of their data.
NR, not reported.
[a]Exponent reported for apparent density.
[b]Results from one-parameter regression model.
[c]Calcium content measured chemically and not ash fraction.

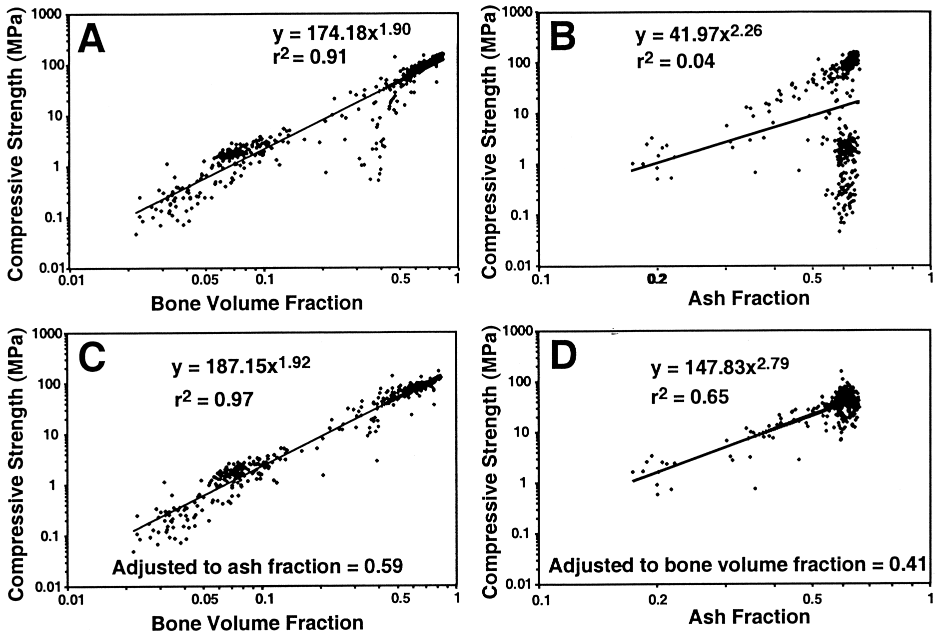

Figure 3. Logarithmic plots of ultimate compressive strength as a function of bone volume fraction (A) and ash fraction (B). The best-fit power law models are also presented. Equation 8 is used to adjust the data to the mean ash fraction (C) (α = 0.59), and the mean bone volume fraction (D) (BV/TV = 0.41). Adjustment improves the predictive strength of the power law models [from r^2 = 0.91 in (A) to r^2 = 0.97 in (C) and from r^2 = 0.04 in (B) to r^2 = 0.65 in (D)].

range of values found in Table 1 (2.0–10.92). The relatively large exponent value found by Schaffler and Burr[23] (10.92) may be a result of the fact that their cortical bovine specimens all had extremely low porosity (0.922 $\leq$ BV/TV $\leq$ 0.971) and all were highly mineralized (0.664 $\leq \alpha \leq$ 0.709). Because the current study did not consider bone within these ranges of bone volume and ash fraction our results may not be comparable to the findings of Schaffler and Burr. If we exclude their results from our analysis we can conclude that the elastic modulus is proportional to the bone volume fraction raised to a power of between 2.0 and 3.5 for the ranges of ash and bone volume fraction examined in the current study.

Several previous studies have suggested that ash fraction is correlated with bone volume fraction (i.e., higher in cortical bone).[6,10] In the present study, we found a poor relationship (r^2 = 0.01) between bone volume fraction and ash fraction.

Given the range in value of ash fraction exponent for the prediction of bone strength it is difficult to predict definitively the influence of ash fraction on bone strength. Depending on the exponent value chosen one could conclude that an increase in ash fraction from 0.65 to 0.68 would cause an increase in strength ranging from 13.4% to 59.0% (**Figure 4**). This wide range suggests that further study of the influence of bone volume and ash fraction is needed. The approximately cubic exponents obtained in the current analysis suggest that small increases in ash fraction may cause large increases in bone strength.

Keller found one-parameter models using the ash density (ash mass/bulk volume) to predict elastic modulus (r^2 = 0.97, percent deviation 46.7%) and strength (r^2 = 0.97, percent deviation 29.9%). He concluded that ash density is the single most effective parameter for the prediction of bone stiffness or strength.[12] A limitation of models using ash density is that it is unclear whether an increase in ash density is the result of increased bone volume fraction or increased ash fraction. This can be important because a change in bone volume fraction may result in different bone material properties as compared with a change in ash fraction, even when the change in ash density is the same. The two-parameter models presented in the current study make this distinction and therefore take into account the mechanical differences between changes in bone volume fraction and changes in ash fraction. For this reason the two-parameter models are more informative than the ash density model even though they are similarly predictive of elastic modulus (r^2 = 0.97, percent deviation 43.4%) and strength (r^2 = 0.97, percent deviation 29.7%).

There are limitations to our study that must be considered. The first limitation pertains to the assumption that the true tissue density (ρ_t) and the ash fraction (α) were related to each other in a simple linear fashion (see equation 5). This assumption is based on a study of healthy human bone.[14] It is possible that future work will identify changes to this relationship that occur in response to some disease states. The linear model (equation 5) may not be as effective under these conditions. Nevertheless, the linear model does explain >65% of the variance in bone volume fraction (r^2 = 0.67; see Figure 2), suggesting that it is effective for most bone samples. The models presented in this study did not consider aspects of trabecular and osteonal architecture and orientation that have been known to influence mechanical prop-

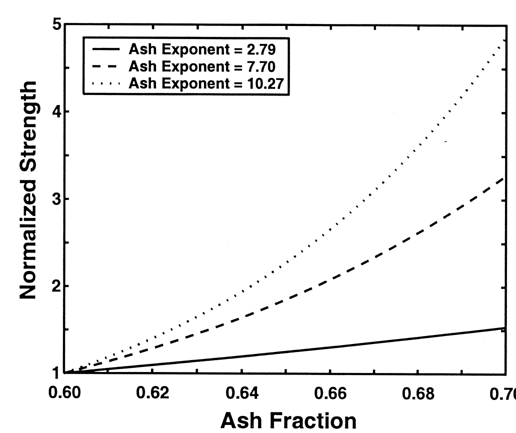

Figure 4. Strength normalized to that at a typical ash fraction value (α = 0.60) is displayed as a function of ash fraction. The ash fraction exponent from the current study (2.79) is compared with that found by Currey[7] (7.7), and Vose and Kubala[24] (10.27).

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erties.[15] Last, some aspects of testing methods were not considered in this study. For example, the data analyzed herein were obtained from compression tests of bone placed directly between metal platens.[12] These methods have been associated with an underestimation of elastic modulus[11,25] that may influence the constants in the elastic modulus model (equation 9).

This study illustrates the predictive power of statistical models that use bone volume fraction and ash fraction to predict bone mechanical properties. We identified ranges for model constants (b and c from equation 2) and recommended future studies to define more accurately the values of some of these parameters. Predictive models of this form (equation 2) may contribute new mechanical perspectives to metabolic bone disease and antiresorptive drug treatment by differentiating the mechanical repercussions caused by changes in ash fraction from those caused by changes in bone volume fraction. Another advantage of this method is that ash fraction and bone volume fraction lend themselves to calculation of areal bone mineral density (BMD), which is the standard method by which osteoporosis is assessed clinically. For this reason future studies may be able to relate ash fraction, bone volume fraction, mechanical properties, and noninvasive BMD measurements in more effective ways than currently available.

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