Journal of Orthopaedic Research

Volume 32, Issue 10
October 2014
Pages 1271–1276

Research Article

Bone mineral density and donor age are not predictive of femoral ring allograft bone mechanical strength

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First published:
7 July 2014 Full publication history

DOI:
10.1002/jor.22679

Citing literature

ABSTRACT

While metal or plastic interbody spinal fusion devices are manufactured to appropriate mechanical standards, mechanical properties of commercially prepared structural allograft bone remain relatively unassessed. Robust models predicting compressive load to failure of structural allograft bone based on easily measured variables would be useful. Three hundred twenty seven femoral rings from 34 cadaver femora were tested to failure in axial compression. Predictive variables included age, gender, bone mineral density (BMD), position along femoral shaft, maximum/minimum wall thickness, outer/inner diameter, and area. We used support vector regression and 10-fold cross-validation to develop robust nonlinear predictive models for load to failure. Model performance was measured by the root-mean-squared-deviation (RMSD) and correlation coefficients (r). A polynomial model using all variables had RMSD = 7.92, $r = 0.84$, indicating excellent performance. A model using all variables except BMD was essentially unchanged (RMSD = 8.12, $r = 0.83$). Eliminating both age and BMD produced a model with RMSD = 8.41, $r = 0.82$, again essentially unchanged. Compressive strength of structural allograft bone can be estimated using easily measured geometric parameters, without including BMD or age. As DEXA is costly and cumbersome, and setting upper age-limits for potential donors reduces the supply, our

results may prove helpful to increase the quality and availability of structural allograft. © 2014 Orthopaedic Research Society. Published by Wiley Periodicals, Inc. J Orthop Res 32:1271–1276, 2014.

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The allograft bone industry is guided by practices intended to optimize safety and effectiveness of allograft bone in numerous clinical applications. Guidelines have been developed and used with respect to avoidance of transmission of neoplastic and infectious disease based on high level scientific data.[1, 2] Adherence to these guidelines has resulted in safe and successful allograft implantation over many years of experience.[3] Despite this excellent track record, the mechanical properties of what is essentially a mechanical device[4] remain comparatively un-assessed. In fact, there are no guidelines prescribed with respect to material properties of structural allograft bone products within the Food and Drug Administration or the American Association of Tissue Banks.[2, 5]

A recent survey of allograft providers demonstrated that given this lack of guidelines, a variety of practices are employed with regard to screening of donors and allografts.[6] On the other hand, interbody spacers manufactured using materials such as carbon fiber, titanium, or polyetheretherketone are expected to have consistent biomechanical properties.[7-9] While the cited advantages of allograft bone over such implants include lower cost and equal or better clinical performance,[10-21] the mechanical performance of structural allograft bone intended for use as an interbody device should be similarly uniform and reliable.

We have accumulated a database of load to failure measurements for femoral ring allograft across multiple donor ages, genders, and graft geometries.[22] Preliminary analysis of this data was limited to linear correlations between these individual parameters and allograft strength. Here, we perform a more rigorous mathematical analysis of this dataset, developing accurate and robust predictive nonlinear models for mechanical strength of the allograft. We hypothesize that features including bone mineral density and donor age are not critical for predicting the compressive strength of structural allograft bone, and could be eliminated from consideration as donor screening variables.

MATERIALS AND METHODS

We employed support vector regression[23] for function estimation within 10-fold cross validation[24] to build and test predictive models for the mechanical strength of allograft bone based on a previously developed database, expanding our previous analysis of this data.[22]

Dataset and Prior Analysis

We have previously reported results on the mechanical strength and related variables of femoral allografts from a dataset[22] that is unique in its size (327 specimens) as well as detail. The specimens were collected from 34 donors who were screened for metabolic and cancer diseases using their medical history and CT scan. For each femoral ring, the data included side (left or right), age of the donor in years (Age), gender of the donor (Sex), and proximal to distal location along the femoral shaft (PD). Minimum and maximum wall thickness in millimeters (MaxWI, MinWI), minimum and maximum diameter in mm (MaxDi, MinDi), and estimated area in mm^2 (Area) were all measured digitally from transverse CT images. Bone mineral density in gm/cm^2 was measured by dual-energy X-ray absorptiometry **(**DEXA) of the femoral head

and neck (BMD).

Mechanical testing methods and preliminary linear analyses of this dataset have previously been discussed.[22] However, relationships between donor variables such as Age, Sex, or proximal–distal location of the allograft, and mechanical strength need not necessarily be linear. A low linear correlation coefficient between load to failure and DEXA, for instance, only indicates that these two quantities are not linearly related; so there potentially may be a nonlinear relationship between the two values, which is not demonstrated by the linear analysis.

A better predictive model of the mechanical strength of the allograft can be developed using values of multiple input variables in a nonlinear analysis. Such predictive models must first be tested for wide applicability and robustness using cross validation.[25] We performed a new analysis of our previously compiled data by employing support vector machines (SVMs) for function estimation,[23] a mathematically sound nonlinear regression technique, under the settings of dataset-wide 10-fold cross validation.[24]

Support Vector Machines and Support Vector Regression

SVMs have been mathematically derived using concepts from the fields of machine learning, statistics, and optimization.[26] They can be thought of intuitively as “machines” that get trained on, or learn structure from, available data so that they generalize well to unknown data. SVMs have been successfully applied to many classification and function prediction tasks, in various fields including science, engineering, and social sciences.[23] SVM-based classification methods have also been used for surgical applications,[27-34] while similar regression techniques have been used to a comparatively lesser extent in medical applications.[35-38] Our analysis was performed using LibSVM[39] (National Taiwan University, http://www.csie.ntu.edu.tw/~cjlin/libsvm/).

Support vector *regression* (SVR) is a method for function estimation that incorporates all the advantages of SVMs.[40, 41] The SVR framework has several advantages over simple linear regression. For example, a variety of linear and nonlinear functional forms, or kernels, can be tested to obtain the best fit in SVR,[42] as opposed to the single linear function available for linear regression. In addition, rather than fitting a surface (or a plane in the linear case), SVR creates a “tube” around the fitted surface, where all points falling inside the tube are considered good fits. This approach allows SVR to implicitly handle noise in data. Thickness of this tube is chosen by the user in order to produce the best predictive performance.

Cross Validation

Cross-validation[24] (CV) is a popular strategy for model selection. The main idea behind CV is to split data, once or several times, to estimate the risk of each model or fit considered. One part of the data (the training sample) is used for training each model. The remaining part (the validation or test sample) is used to estimate the risk of failure of the model. CV then selects the model with the smallest estimated failure risk. CV avoids overfitting because the training sample is independent from the validation sample.[24]

We employed the commonly used format of 10-fold CV to analyze the allograft data. We randomly divided the dataset of 327 allografts into 10 parts of close to equal size, 7 folds of 33 specimens and 3 folds of 32 specimens each. We then used 9 out of the 10 folds to fit an SVR model predicting the maximum allograft strength in KN using either all available variables, or subsets of the predictive variables, as inputs. Each input variable except Sex was standardized to the range [0,1] before this analysis. These fitted models were then used to predict the maximum strength of allografts in the remaining (10th) test fold. Since, the model is built independently of the allograft data in the 10th test fold, there is no chance of overfitting. We repeated this

procedure for each of the 10 folds, thus generating predictions for all 327 allografts.

The performance of the model is then evaluated by computing the root mean squared deviation (RMSD) between the actual and predicted values of maximum strength (lower value indicates better fit), and the Pearson correlation coefficient (r) between these two sets of values (higher r indicates better fit). The RMSD between the actual values S_j and predicted values $\hat{S}_j$ of mechanical strength is defined as

$$\mathrm{RMSD} = \sqrt{\frac{\sum_{j=1}^{n} (S_j - \hat{S}_j)^2}{n}}$$

for $n = 327$ (the sample size). We tested four kernel options—linear, polynomial (degree 2–4), radial basis function (RBF), and sigmoid. For each kernel, we tried values comprising the entire range for each parameter that can be selected by the user. For each subset of input variables, we evaluated more than 100,000 (10^5) candidate models in this manner, and chose the one with the smallest RMSD, or equivalently, the largest r value, as the best predictive model.

We tested all input variables together, as well as each variable individually. We then considered subsets of inputs that leave out the less predictive variables, and repeated the process. To compare two predictive models with correlations r and r' for the same dataset, we converted these values to Fisher correlations[43, 44] r_F and r'_F using the formula $r_F = \tanh^{-1}(r)$, and then computed the associated Z-statistic and the corresponding p-value using

$$Z = \frac{r_F - r'_F}{\sqrt{2/(n-3)}}, \tag{1}$$

where n is the sample size (327 for the entire dataset). The null hypothesis here is that the candidate model (r') performs as well as the best model (r), and we accept or reject this hypothesis using the one-sided p-value associated with the Z-statistic.

The 327 allografts came from 175 male and 152 female donors. We repeated the above analysis separately for these two subsets. We compared the best models for male and female specimens using the following Z-statistic for the null hypothesis that a candidate model performs as well as the best male model:

$$Z = \frac{r_F - r'_F}{\sqrt{(1/(n-3)) + (1/(n'-3))}}, \tag{2}$$

where $n = 175$ and $n' = 152$. Here, r_F and r'_F are the Fisher correlation coefficients for the male and female models, respectively.

RESULTS

Results for the entire dataset (327 allografts) are summarized in Tables 1 and 2. Details are provided for the best model under each selection of variables. The maximum load values vary from 9.45 to 83.30 KN, with a mean ± SD of 42.31 ± 14.65 KN.

Table 1. Best Predictive Models for the Entire Dataset Using Individual Variables

Model	Kernel	RMSD	*r*	*p*-Value
PD	RBF	12.01	0.57	0.00
Age	RBF	12.56	0.52	0.00
BMD	RBF	12.08	0.56	0.00
MaxWI	Sigmoid	9.76	0.75	0.00
MinWI	Sigmoid	9.96	0.73	0.00
MaxDi	RBF	13.37	0.41	0.00
MinDi	RBF	13.40	0.40	0.00
Area	Sigmoid	8.92	0.79	0.03
Sex	Poly ($d = 4$)	13.15	0.44	0.00

p-Values are for comparison to the best model using all variables listed in Table 2 (see Equation (1)). PD is the proximal–distal position along the femoral shaft, BMD is bone mineral density, MaxWI (MinWI) is the maximum (minimum) wall thickness, and MaxDi (MinDi) is the maximum (minimum) diameter of the allograft. Kernel specifies the type of nonlinear function that provided the best model. RBF stands for radial basis function. Lower RMSD values (and higher r values) indicate better predictive models. MaxWI, MinWI, and Area are the strongest predictive variables as shown by the lower RMSD values.

Table 2. Best Predictive Models for the Entire Dataset Using Various Combinations of Variables

Model	Kernel	RMSD	*r*	*p*-Value
All variables	Poly ($d = 4$)	7.92	0.84	—
All variables except BMD	RBF	8.12	0.83	0.35
All variables except BMD and Age	RBF	8.41	0.82	0.18
MaxWI, MinWI, Area	Poly ($d = 4$)	8.61	0.81	0.10

p-Values are for comparison to the best model using all variables (see Equation (1)). Poly stands for polynomial kernel with degree d. See Table 1 for explanation of other terms.

We first developed predictive models using individual variables (Table 1). We compared the predictive performance of the best model using each variable to that of the best model using all variables (listed in Table 2). None of the individual variables was as predictive as the collection of all variables. Among the individual variables, maximum and minimum wall thickness and transverse graft area were more predictive than the rest

of the variables (RMSD of 9.96 or less as compared to 12.01 or more for all other variables).

Predictive models using individual variables performed statistically significantly worse than the best model using all variables. This demonstrates that combinations of variables will result in better predictive models than using variables individually.

We then developed predictive models using all variables, and also using several subsets of variables (Table 2). A polynomial model of degree 4 using all variables showed the best predictive performance, resulting in an RMSD of 7.92 KN and r value of 0.84 under 10-fold CV. Leaving out BMD, or both BMD and Age, results in slightly worse models, that is, with higher RMSD and smaller r values, although these differences in model performance were not statistically significant ($p = 0.35$ and $p = 0.18$, respectively).

For each choice of predictive variables, the best models using linear kernels performed statistically significantly worse ($p < 0.05$) than the corresponding best nonlinear model, except in the case of Sex (Table 3). For Sex, the best linear and best nonlinear models performed essentially identically ($p = 0.42$), although both models were not good predictors. Our results thus demonstrate that nonlinear predictive models are generally more accurate than linear models. The best predictive models fitted on the entire data set using the optimal choice of parameters identified for each choice of variables listed in Tables 1 and 2 are made available on the internet at http://www.math.wsu.edu/faculty/bkrishna/Allograft.

Table 3. Comparison of Best Model Using Linear Kernel to the Best Model Using Nonlinear Kernel for Various Individual and Combinations of Variables, for the Whole Set of Specimens

Model	RMSD	*r*	*p* -Value
Individual variables			
PD	13.38	0.40	0.00
Age	14.62	0.03	0.00
BMD	14.58	0.09	0.00
MaxWI	10.57	0.68	0.03
MinWI	10.98	0.66	0.03
MaxDi	14.66	–0.01	0.00
MinDi	14.64	0.02	0.00
Area	9.61	0.74	0.04
Sex	13.71	0.43	0.42
Combinations of variables			

p -Values listed are for comparison to the corresponding best non-linear model listed in Tables 1 and 2 (using Equation (1)).

Model	RMSD	*r*	*p*-Value
All variables	8.73	0.80	0.049
All variables except BMD	8.85	0.78	0.03
All variables except BMD and Age	8.91	0.76	0.04
MaxWl, MinWl, Area	8.95	0.76	0.04

p-Values listed are for comparison to the corresponding best non-linear model listed in Tables 1 and 2 (using Equation (1)).

Single Donor Exclusion Cross Validation

The 327 allograft samples were taken from 34 donors. To insure that our conclusions were not affected by any pseudoreplication effects, we repeated the analyses using 34-fold CV, with the samples from each donor put in a separate fold (instead of randomly dividing the data set into 10 folds). The results presented in Table 4 show that similar results occur as with the 10-fold CV. In particular, Age and BMD were not good predictors in this setting as well.

Table 4. Best Predictive Models for the Entire Dataset Under Single Donor Exclusion Cross Validation (Using 34 Folds)

Model	Kernel	RMSD	*r*	*p*-Value
PD	RBF	12.06	0.57	0.00
Age	RBF	14.49	0.26	0.00
BMD	Sigmoid	14.11	0.27	0.00
MaxWl	Sigmoid	9.84	0.74	0.04
MinWl	Sigmoid	10.01	0.73	0.02
MaxDi	RBF	13.69	0.36	0.00
MinDi	RBF	13.60	0.38	0.00
Area	Sigmoid	9.00	0.79	0.40
Sex	Linear	13.71	0.42	0.00
All variables	Poly ($d = 2$)	8.88	0.80	0.46

p-Values are for comparison to the best model using all variables except Age and BMD. See Table 1 for explanation of other terms.

Model	Kernel	RMSD	*r*	*p*-Value
All variables except BMD	RBF	8.94	0.79	0.42
All variables except BMD and Age	RBF	8.82	0.80	—

p-Values are for comparison to the best model using all variables except Age and BMD. See Table 1 for explanation of other terms.

Models for Male and Female Specimens

Even though Sex was not a good predictor (see Table 1), we repeated the analysis separately for the 175 allografts from male donors and 152 specimens from female donors. We observed the same trends within each subset as with the overall dataset—BMD and Age were not strong predictors, and performances of best models leaving BMD and Age out were not significantly different from the best model using all variables. However, the best female model did perform significantly better than the best male model (Table 5). Similar trends were observed for models using subsets of variables of interest as well—the RMSD and *r* values for the female models were always significantly better than the corresponding male models.

Table 5. Best Predictive Models for Male and Female Specimens Using Various Subsets of Variables

Model	Kernel	RMSD	*r*	*p*-Value
Male, all variables	RBF	9.22	0.76	—
Male, all variables except BMD	RBF	9.28	0.75	0.47
Male, all variables except BMD and Age	RBF	9.41	0.74	0.40
Female, all variables	RBF	6.31	0.85	0.01
Female, all variables except BMD	RBF	6.44	0.84	0.02
Female, all variables except BMD and Age	RBF	6.95	0.82	0.07

The *p*-value is for comparison to the best model for male specimens using all variables (Equation (1) for comparing two models for male specimens, and Equation (2) for comparing models for male and female specimens). See Table 1 for explanation of terms.

DISCUSSION

Using comprehensive mathematical analysis, we have developed accurate and robust predictive models for the mechanical strength of allograft bone. While a nonlinear polynomial model using all nine variables

performed the best, models leaving out BMD and donor age performed nearly as well as the best model using all variables. Furthermore, neither age nor BMD were good predictors of mechanical strength individually.

These results extend our prior analysis.[22] Our prior report used separate single variable linear correlations, and may underestimate the importance of specific variables as part of a multivariate predictive formula. The analysis presented here shows more definitely that age and BMD are not required for predicting the strength of structural allograft bone. While our best-fit model results in an $r^2 = 0.71$, this statistic has a different meaning in this analysis than it would for a linear regression of the entire dataset. While our analysis may not include all predictive variables of importance, we were at least able to verify the limited impact of donor age and BMD.

These findings may have importance to allograft bone providers. Measurement of the BMD of potential allograft bone donors would be time consuming and costly. Our results suggest that such a step is not needed, at least from the standpoint of mechanical performance. Perhaps even more importantly, our results suggest that donor age does not negatively impact bulk allograft strength. Many allograft providers currently enforce an upper age limit for structural allograft bone donors.[6] Our results again demonstrate that considerations of graft strength do not require such age limits. Relaxation of upper age limit for donors may thus be one opportunity to increase the available supply of clinically used structural allograft bone.

The highly predictive geometric features, including maximum and minimum wall thickness and allograft area, could be measured either digitally from CT scans or directly at the time of harvest. Ultimately, allograft providers and regulatory agencies must determine whether these results warrant an effort to change current practice. We do not expect that these results eliminate the need for further mechanical assessments of allograft bone. In particular, the differences in model performances found relating to gender may require further experimental results to be fully understood. Further assessments of mechanical effects following sterilization or irradiation would also extend the potential value of our results.

This study shares some limitations with our previous report.[22] For one thing, quasi-static strength testing does not evaluate the mechanical strength of allograft under the repetitive loading and remodeling, which occur during healing. In addition, any analysis based solely on biomechanical testing cannot predict clinical performance. Donor age or BMD could have impacts on biological viability for bone healing independent of mechanical properties. Thus, evaluation of biological properties of structural allograft as a function of age and BMD would be important before considering any change to current tissue bank practices. On the other hand, sufficient mechanical strength is a first prerequisite for interbody graft suitability for clinical use.

In conclusion, our results strongly support the idea that age and BMD are not critical factors in predicting mechanical performance of structural femoral ring allograft. Clinical studies are an important next step before using these findings as a basis for guidelines for use by allograft bone providers.

ACKNOWLEDGMENTS

The authors acknowledge the contributions of J. Rafe Sales, MD, Jeremy Tesar, MD, and Timothy Bahney, PE, to this study. There was no financial support for this study, and there are no professional or financial affiliations that directly or indirectly bias our results. Krishnamoorthy acknowledges partial support from the National Science Foundation via grant 1064600.

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