Statistical Analysis Plan

A Prospective Study of Human Bone Adaptation Using a Novel in Vivo Loading Model

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Statistics and Expected Outcomes:

An intent to treat analysis will not be employed here because the purpose of this research is to determine the link between *actual strains applied to bone* and the bone adaptive response. The present study is not intended to address the degree to which mechanical loading is an effective means to improve bone strength in a public health setting. Accordingly, adherence to the mechanical loading protocol is expected to influence the degree of adaptation and will be considered a potential explanatory variable for the following analyses.

For Experiment 1, hypotheses are related to the effect of strain magnitude.

For Experiment 2, hypotheses are related to the effect of strain rate. In both cases, the statistical analysis plan is the same, but tests will be performed on the corresponding variables (strain magnitude, or strain rate).

Hypothesis 1a: Bone mass will increase proportionally to the applied strain.

This hypothesis will be tested in two ways. In the first analysis, subjects will be analyzed by group (control, low, and high strain magnitude groups). For the group analysis, the 12-month change in whole radius total BMC will be analyzed as the primary dependent variable in a linear regression model with coefficients representing contrasts between each of the two experimental groups and the control group. Secondary outcome measures of trabecular BMC, ultra-distal BMC, fracture strength, moments of inertia, and others, will also be compared between groups using regression models for change scores at each of the four time points.

If our hypothesis is supported then there will be little change in the control group, a small but significantly higher increase in the 1800 με group, and a large and significantly higher increase in the 3600 με group. Similar models will be fit predicting change from baseline to 3, 6, and 9 months.

In the second analysis, we will consider the *actual* strain magnitudes achieved by each subject, (which may differ from the group assigned strain), as a continuous variable, and will set the strain magnitude for control subjects to zero. The underlying assumption in doing this is that the baseline daily activity for *all* subjects is approximately equal, and is sufficient to maintain bone homeostasis. For this analysis, all four time points will be combined into a single model to examine changes across time after the loading regime has ended, and to compare the levels of applied strain. The dependent variable is the change score (in whole radius total BMC) from baseline; the independent variables are level of strain, time (3, 6, 9, 12 months), and a random intercept term for each subject to handle collinearity within repeated measurements. As in the first analysis method, secondary outcome measures of regional BMC, fracture strength, and others, will be considered as well.

If our hypothesis is supported then strain magnitude will be a significant predictor of change in whole radius total BMC and other related variables.

Hypothesis 1b: High initial bone mass, physical activity levels, and grip strength will be associated with diminished adaptive response for a given strain magnitude.

To test this hypothesis, initial BMC, grip strength, and physical activity will be added as potential covariates for the statistical models described in Hypothesis 1a.

If our hypothesis is supported then we would expect to observe an inverse relationship (negative coefficient) between initial bone mass, physical activity, grip strength, and change in BMC per group or per unit applied strain.

Hypothesis 1c: Bone structural changes will include increases in cortical diameter and thickness, and increased trabecular bone mass near the endosteal surface.

To test this hypothesis, the following variables will be examined:

For cortical diameter and thickness: integral and cortical bone mass and bone volume, compressive and bending strength index, and cross-sectional moments of inertia (bending and torsional)

For trabecular bone: trabecular bone mass and volume, cross sectional trabecular moments of inertia

Using the methods described for testing hypothesis 1a, changes in each of the specific variables listed will be examined at each time point. Here, the primary interest is in which specific quantities show the largest strain-related change.

If our hypothesis is supported, we would expect to observe significant strain-dependant increases in each of the variables listed for the experimental groups, but not in the control group.

Hypothesis 1d: Local regions experiencing high strain magnitudes will experience greater local increases in BMC than regions experiencing low strain magnitudes.

This hypothesis will be tested using only subjects in the experimental conditions. For each subject, all of the elements within the baseline FE model will be divided into quartiles based on actual Von Mises equivalent strain occurring within each element. Of interest for the present analysis are elements in the highest strain quartile and the lowest strain quartile. (Note that Von Mises equivalent strains always have a positive sign.) For each of these quartile groups the change in QCT voxel density for those voxels corresponding to the location of the elements will be determined. We will use a Student's t-test to compare the average voxel density change in high strain versus low strain quartiles.

If our hypothesis is supported then elements experiencing the highest Von Mises strain will have significantly greater increases in density compared to elements experiencing the lowest Von Mises strain. Our underlying assumption in using the highest and lowest quartiles is that a minimum strain threshold is required to initiate an increase in density. Therefore, including all elements in the analysis, most of which do not exceed this threshold, may make it difficult to detect a local effect, if one is present.