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14. ABSTRACT

There is no established treatment to prevent bone loss or to induce new bone formation following SCI, although the risk is high in this population of osteoporosis-related bone fracture. This study aims to learn if the severe osteoporosis in lower extremities caused by spinal cord injuries can be slowed or reversed with a combination of an exercise that simulates weight-bearing and a bisphosphonate medication. 70 Individuals with T3-12 spinal cord injuries will be enrolled in a 12-month regime of adapted FES-rowing. Our preliminary study findings demonstrated this exercise led to new bone formation and improved bone micro architecture in the lower extremities of people with SCI. Half of the subjects also receive a bisphosphonate medication known to slow bone loss, but not stimulate bone renewal.

Participant recruitment began in late February, 2011, and is complete. We have enrolled 70 subjects, 11 of which have completed the study.

15. SUBJECT TERMS
SCI, Osteoporosis, FES-rowing, zoledronic acid, exercise, bone health

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Table of Contents

Introduction

Serious spinal cord injury (SCI) causes osteoporosis in the lower extremities, significantly increasing the risk of bone fracture in this population. However, there currently is no established treatment to prevent bone loss or to induce new bone formation following SCI.

The goal of this clinical trial -- *FES-Rowing versus Zoledronic Acid to Improve Bone Health in SCI* – is to develop an evidence-based therapeutic protocol to address a prevalent and significant health issue in this population. A second aim is to better understand the bone biology and bone health of people with serious SCI.

The trial calls for 70 subjects with SCI to participate in a 12-month adapted FES-rowing program. Half of the subjects also receive a one-time infusion of zoledronic acid, a bisphosphonate used to treat osteoporosis, usually in older women.

We demonstrated in our preliminary studies that functional electrical stimulation (FES) rowing stimulates bone formation and improved bone micro-architecture in the lower extremity. Bisphosphonate medications slow bone loss but do not stimulate new bone formation. Therefore, combination treatment with a bone-building stimulus (FES-rowing) and a medication that stops bone loss (bisphosphonate) may result in greater improvements in bone compared to either agent alone. We are using DXA and CT bone scans to compare changes in bone density and health pre- and post-rowing and bisphosphonate treatment. The results of this study should provide a better understanding of possible therapies to maintain bone strength among people with SCI.

Body

We received final Department of Defense approval to begin active subject recruiting in February, 2011. In the past year we have focused on recruitment and enrollment, row training, and data collection. We have completed study enrollment, enrolling 70 subjects. Among the enrolled subjects, 11 have completed end of study testing, 24 have finished strength training and begun the 12-months rowing program and 15 have received the zoledronic acid infusion. We expect 8 more to complete the study over the next 3-6 months.

Statement of Work, Task 1: Study preparation, human subjects approval, finalize instruments, procedures, protocols; research coordinators

This task was completed during the first year of the study.

Statement of Work, Task 2: Recruitment and screening

We have reached our subject enrollment goal of 70 and are no longer recruiting or screening potential subjects.

Statement of Work, Task 3: Enrollment, randomization, baseline testing

We have enrolled 70 individuals, 35 in treatment arm and 35 in the rowing only arm.

Baseline bone density scanning, blood draws (renal function, vitamin D levels, calcium levels, bone turnover markers), and distribution of calcium and vitamin D supplements have been carried out successfully at the VA Boston Healthcare-Jamaica Plain Campus. Among participants who have been tested as of October, 2013, 30 were found to have a vitamin D deficiency (<than 30ng/ml) and were treated with supplemental vitamin D. No subject has been excluded from participation based on screening blood work (i.e. renal function has been adequate in all subjects).

Statement of Work, Task 4: 6-month measurements

34 subjects have had their midpoint data collection – bone density scans, as well as blood draws to check vitamin D, renal function, and future analysis of bone turnover markers.

12 subjects have had their 6 month of rowing CT scan of the knee.

Statement of Work, Task 5: FES-row training

24 subjects are currently active rowing. We anticipate 5 more will enter the rowing phase in the next 2-3 months.

Statement of Work, Task 6: Zoledronic acid infusion

Fifteen subjects have received the zoledronic acid infusion at the VA Boston Healthcare-Jamaica Plain Campus. The nurse practitioner who administered the infusion makes follow-up phone calls within 24 hours to check on how the subject is feeling. 20 additional subjects have been randomized to the treatment arm of the study and will receive the infusion once strength training is complete.

Statement of Work, Task 7: 18-month measurements

We completed final testing on 11 subjects and have scheduled final testing for 2 subjects who have completed 1 year of rowing. We expect 7 more to complete the study over the next 3-6 months. We expect 15 additional subjects to complete the study over the next 12 months.

Statement of Work, Task 8: Data analysis

We are currently analyzing cross-sectional data collected for the all subjects enrolled, including baseline biomarkers and CT data on 44 subjects and longitudinal CT data on 16 participants who have completed at least 6 months of rowing.

Key Research Accomplishments

This is an intervention study focused on bone outcomes. Given that a cycle of bone remodeling is 3 months, our main outcomes are at 1 year after initiation of training. A period of strength training is required before the initiation of the 1-year period and this can vary from 2 weeks to several months. We have begun writing a manuscript for submission looking at baseline CT scans of the knee and biomarker results. Below we detail our preliminary findings to date. Biomarker analysis is done in batches to limit variability.

Preliminary Findings to Date:
As of October 2013, we have completed enrollment of 70 participants, 35 to the zoledronic acid infusion arm and 35 to the exercise only arm. Of those enrolled there are 63 males and 7 females. There are 14 motor incomplete injuries and 53 motor complete injures. The mean age was 38.7 (20.7-65.1) and the mean years post injury was 10.4 (0.08-37.5). A total of 60 have had baseline blood work and DXA scan and 44 have had their baseline CT. A total of 34 have had their midpoint blood work and DXA scan. A total of 12 have had their 6 month CT scan. 10 have had end of study blood work and DXA scan and 8 have had their end of study CT scan.

Subject Characteristics:

Variable	ZA Infusion and Exercise Arm n=35	Exercise Only Arm n=35
Demographics		
Age (Mean ± SD) [years]	37.2 ± 12.7	40.1 ± 11.3
Age (Range) [years]	20.7-63.5	21.1-65.1
White %	27 (77.1%)	30 (85.7%)
Male %	32 (91.4%)	31 (88.6%)
Duration of SCI (Mean ± SD) [years]	9.9 ± 10.8	10.9 ± 10.47
Duration of SCI (Range) [years]	0.08-37.53	0.13-37.2
Motor Complete Injury %	28 (80.0%)	25 (71.4%)
BMI [Mean ± SD] (kg/m^2)	25.2 ± 5.6	27.6 ± 5.6
Vitamin D (Mean ± SD)	29.6 ± 10.3	26.6 ± 10.6
• Deficient <30 ng/ml	18 (60.0%)	18 (64.3%)
• Sufficient ≥30 ng/ml	10 (40.0%)	12 (35.7%)
Smoking History		
• Current smoker	3 (10.0%)	3 (10.3%)
• Former smoker	8 (26.7%)	8 (27.6%)
• Never smoker	19 (63.3%)	18 (62.1%)

We scanned at traditional bone density sites (femoral neck, total hip and radius) as well as SCI specific skeletal sites (distal femur and proximal tibia) as these are the sites were fractures are most common within the SCI population. For subjects age 50 or older, T-score was used to classify hip bone density (total hip and femoral neck) according to the World Health Organization (WHO) definitions of normal (T-score $\geq$-1), osteopenia (T-score <-1 and >-2.5) and osteoporosis (T-score $\leq$-2.5). For subjects under the age of 50, Z-score was used to classify hip bone density as normal (Z-score >-2) or as lower than expected for age and sex (Z-score $\leq$ -2). A total of 41% of the participants were classified as having osteoporosis/BMD lower than expected for age.

Bone Mineral Density (Mean ± SD) (Range) [g/cm^2]		
SCI Specific Sites		
• Distal femur	0.782 ± 0.24	0.691 ± 0.24
• Proximal tibia	0.821 ± 0.31	0.694 ± 0.22
Traditional Sites		
• Femoral Neck	0.867 ± 0.22	0.759 ± 0.19
• Total Hip	0.851 ± 0.24	0.748 ± 0.21
• Radius	0.999 ± 0.08	0.982 ± 0.08
Osteoporosis status		
• Normal	11 (31.4%)	8 (22.9%)
• Osteopenia	3 (8.6%)	1 (2.8%)
• Osteoporosis/BMD lower than expected for age	12 (34.3%)	17 (48.6%)
• No hip BMD available	9 (25.7%)	9 (25.7%)

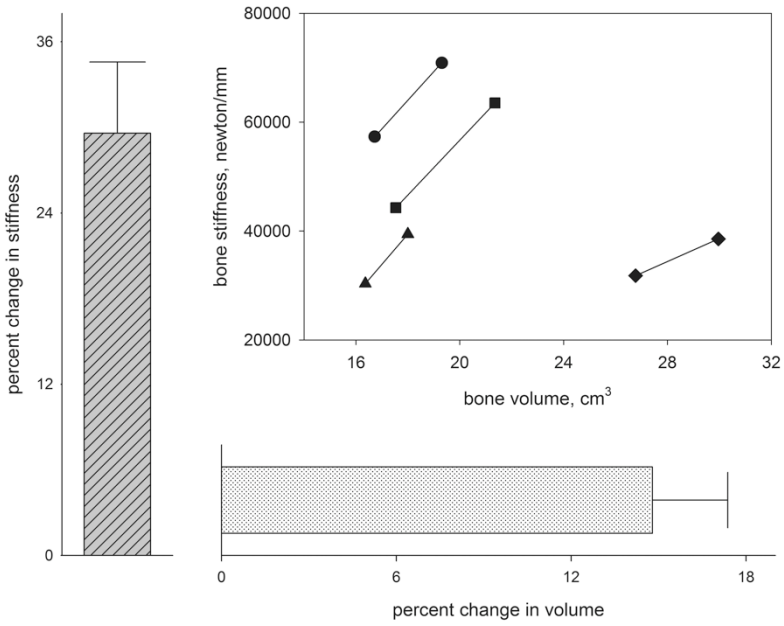
Baseline Vitamin D Status:

Of those tested, 36 were found to have a vitamin D deficiency (< than 30 ng/ml) and were treated with supplemental vitamin D. After completing the round of repletion, 14 had corrected vitamin D levels greater than 30 ng/ml. After repletion, everyone takes a standard dose of vitamin D and calcium. The average vitamin D value was 28.1 ng/ml (std=10.48, range 7-58.7).

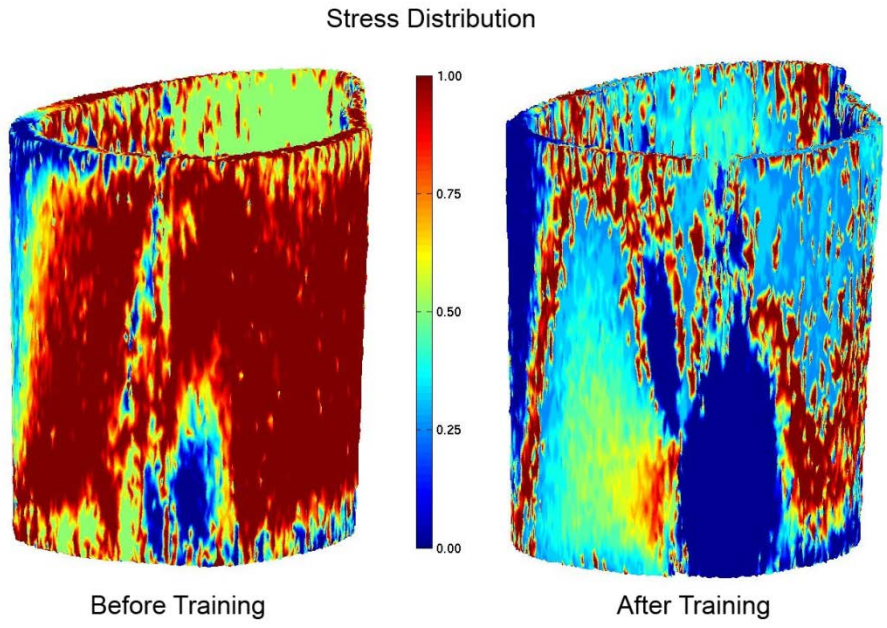
Improvements in Bone Stiffness:

Finite element analysis of CT scans is ongoing to calculate changes in bone volume and bone stiffness in response to rowing. A 3D model of the proximal tibia was created from the volumetric CT images. A 10 mm section of the proximal tibia was segmented from the surrounding tissue by thresholding followed by region

growing. The model was meshed with tetrahedral elements and linear elastic material properties for bone were assigned to the model (Young's Modulus, E, of 17kGPa and a Poisson's ratio of 0.3). After boundary conditions were assigned, the bottom of the tibia was fixed in space and the top was compressed by 0.1 mm in axial direction. Stiffness was determined by recording the sum of the reaction forces of all elements and dividing it by the displacement (k=F/x). Preliminary findings indicate increases in bone volume and stiffness in response to rowing. We anticipate being able to assess for differences in gains in bone strength based on zoledronic acid treatment in the coming 6 months.



FES rowing results in increased tibial bone volume and stiffness. Bone stiffness was plotted as a function of volume for four SCI subjects (●, ■, ▲ and ◆) after 6 months of row-training. Rowing increased stiffness and volume in all four subjects**.**



FES rowing improves tibial stress distribution. This image demonstrates the change in stress distribution in response to the same axial force (10 kN) at the tibia in the same subject before and after FES-row training. Stress values are normalized to 0 - 1 (0: blue, no stress to 1: red, max stress). The overall stiffness of the bone (i.e., its ability to withstand axial compression) was improved by almost 50%, from ~43 to ~64 kN/mm). This indicates improved bone strength and better stress distribution.

Adiponectin is negatively associated with baseline femur stiffness and maximal load

We analyzed the associated between various bone biomarkers and bone strength at the baseline scan. Femur stiffness and maximal load were not normally distributed so the natural log of these values was used. We

found adiponectin to be negatively associated with femur stiffness ($p<0.0001$, $R^2=0.47$) and maximal load ($p=0.0003$, $R^2=0.42$). The association remained after controlling for years post injury (femur stiffness $R^2=0.55$ and maximal load $R^2=0.56$). We are currently preparing a manuscript with these findings.

Reportable Outcomes

The following work was presented at national or international conferences in the past year. This work is directly related to the study aims:

Dr. Morse presented preliminary findings in a course at the 2013 ASIA conference in Chicago. This talk was entitled, "*Bone Regenerative Effects of FES-Rowing"*.

Conclusion

We have ended the third year of the study with great success in recruitment and testing. We have completed our enrollment goal of 70 participants. We are successfully row-training subjects and have administered zoledronic acid infusions without adverse events. Our research team is productive, efficient, and communicates well to complete study tasks. We have presented our preliminary findings at national and international conferences with good reception.

References

Not applicable.

Appendices

None.