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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 was completed in October 2013. We have enrolled 70 subjects, 46 of whom have completed the study.

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

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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 resolution of institutional conflicts with the VA site. We have copmleted all study testing and are now focusing on completion of data analysis.

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 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. 36 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 (ie renal function has been adequate in all subjects).

Please see table below for characteristics of enrolled participants based on randomization arm.

Subject Characteristics:

Variable	ZA Infusion and Exercise Arm n=34	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 (77.14%)	30 (85.71%)
Male %	32 (91.43%)	31 (88.57%)
Duration of SCI (Mean ± SD) [years]	9.93 ± 10.8	10.9 ± 10.5
Duration of SCI (Range) [years]	8.1-46.1	0.13-37.3
Motor Complete Injury %	28 (52.24%)	25 (71.43%)
BMI [Mean ± SD] (kg/m^2)	25.2 ± 5.6	27.5 ± 5.6
Vitamin D (Mean ± SD)	29.6 ± 10.3	26.6 ± 10.6
• Deficient <30 ng/ml	23 (65.71%)	25 (71.43%)
• Sufficient ≥30 ng/ml	12 (34.29%)	10 (28.57%)
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%)

Statement of Work, Task 4: 6-month measurements

6-month measurements are complete. 37 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. 20 subjects have had their 6 month of rowing CT scan of the knee.

Statement of Work, Task 5: FES-row training

FES-row training is complete. 38 subjects transitioned from strength-training to active rowing.

Statement of Work, Task 6: Zoledronic acid infusion

All zoledronic acid infusions are complete. Eighteen 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.

Statement of Work, Task 7: 18-month measurements

We completed final testing for all participants.

Statement of Work, Task 8: Data analysis

We completed cross-sectional analysis of baseline DXA and CT data collected for the all subjects enrolled.

Baseline Bone Density/Incidence of Osteoporosis at the Hip: We scanned 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 ≥-1), osteopenia (T-score <-1 and >-2.5) and osteoporosis (T-score ≤-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 ≤ -2). A total of 30.0% of the participants were

classified as having osteoporosis/BMD lower than expected for age. Four participants had no hip data available for analysis due to contracture and 3 are pending DXA scans.

Bone Mineral Density (Mean ± SD) (Range) [g/cm^2]		
SCI Specific Sites		
• Distal femur	0.756 ± 0.24	0.715 ± 0.25
• Proximal tibia	0.795 ± 0.30	0.733 ± 0.26
Traditional Sites		
• Femoral Neck	0.859 ± 0.21	0.795 ± 0.23
• Total Hip	0.834 ± 0.23	0.780 ± 0.23
• Radius	0.980 ± 0.09	0.985 ± 0.08
Osteoporosis status		
• Normal	9 (25.7%)	7 (20.0%)
• Osteopenia	12 (34.3%)	9 (25.7%)
• Osteoporosis/BMD lower than expected for age	9 (25.7%)	12 (34.3%)
• No hip BMD available	5 (14.3%)	6 (17.1%)

Baseline Vitamin D Status: Of those tested, 36 were found to have a vitamin D deficiency (<than 30ng/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).

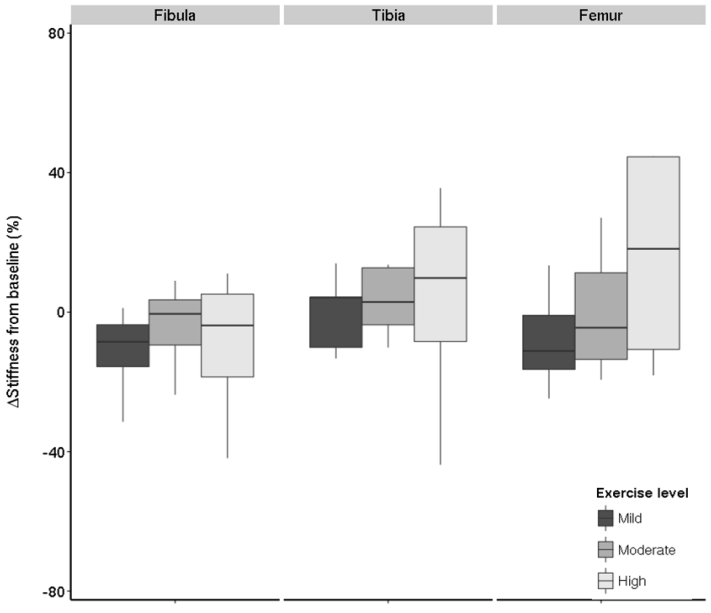
Adiponectin as a marker of bone strength and fracture history in motor complete SCI: We explored the association between circulating adiponectin levels and bone strength in 27 men who had completed baseline testing. Plasma adiponectin levels were quantified by ELISA assay. Axial stiffness and maximal load to fracture of the distal femur were quantified via finite element analysis using reconstructed 3D models of volumetric CT scans. We also collected information on timing, location, and cause of previous fractures. Axial stiffness and maximal load were inversely associated with circulating adiponectin levels (R^2=0.32, p=0.002; R2=0.33, p=0.002) after adjusting for injury duration and lower extremity lean mass. In individuals with post-SCI osteoporotic fractures, distal femur stiffness (p=0.01) and maximal load (p=0.005) were lower and adiponectin was higher (p=0.04) than those with no fracture history. Based on these findings, strength estimates may improve fracture risk prediction and detection of response to osteogenic therapies following spinal cord injury. Furthermore, our findings suggest that circulating adiponectin may indeed be a feasible biomarker for bone health and osteoporotic fracture risk in individuals with motor complete spinal cord injury. These findings will were reported in a recent publication (Adiponectin is Associated with Bone Strength and Fracture History in Paralyzed Men with Spinal Cord Injury. Osteoporos Int. 2014 Nov;25(11):2599-607).

FES-rowing and aerobic capacity: We hypothesized that hybrid Functional Electrical Stimulation Row Training (FES-RT) would improve aerobic capacity but that it would remain strongly linked to level of spinal cord lesion due to limited maximal ventilation. We studied 14 participants with complete SCI T3_T11, >2 years post-injury, aged 21-63 years after six months of FES-row-training. We found that FES-row training significantly increased VO_2peak and Vepeak (both p<0.05). Prior to FES-row training, there was a close relationship between level of spinal cord injury and VO_2peak (adj r^2=0.40, p=0.009) that was markedly reduced after FES-row training (adj r^2=0.15, p=0.10). In contrast, the relationship between level of injury and $V_E$peak was comparable before and after FES-RT (adj r^2=0.38 vs. adj r^2=0.32, both p<0.05). Therefore, we conclude the increased aerobic capacity reflects more than increased ventilation; FES-row training effectively circumvents

the effect of the spinal cord injury on peak aerobic capacity by engaging more muscle mass for training, independent of level of injury.

Improvements in Bone Stiffness is Exercise Dose-Dependent: We analyzed lower extremity CT scans obtained at baseline (all volunteers) and after 6 (n = 18) or 12 months (n = 29) of exercise (n=17 at all three time points).

	Exercise only (n=16)	Exercise + ZA (n=13)
Sex (M/F)	15/1	12/1
Age	38 ± 3	36 ± 4
BMI (kg/m²)	26.9 ± 1.4	24.0 ± 1.5
Age at injury	25 ± 2	28 ± 3
Injury duration (years)	13 ± 3	8 ± 3
Injury severity (A/B/C)	9/3/4	9/3/1
25OH Vitamin D	26.4 ± 2.3	34.3 ± 2.5*
Tibia BMD	0.79 ± 0.07	0.82 ± 0.08
Femur BMD	0.77 ± 0.08	0.76 ± 0.09



Axial stiffness of the proximal fibula (non-weight-bearing bone, reflecting the effect of ZA treatment alone), and proximal tibia and distal femur (reflective of weight-bearing and ZA treatment) were quantified via finite element analysis using reconstructed 3D models of volumetric CT scans. Effects of ZA treatment, exercise, and time were assessed via a linear mixed-effect model, repeated on each side (dominant vs non-dominant) nested within each subject with a random intercept, taking into account correlations between each bone within each side and subject. We found a time-dependent decline in fibula stiffness, which was prevented by ZA treatment (treatment x time effect $p < 0.01$). In contrast to the fibula, there was no decline in tibia stiffness for either rowing-only or rowing plus ZA treatment ($p > 0.2$ for time, treatment, or interaction effects), suggesting that both ZA treatment and exercise were effective at preventing bone loss.

Furthermore, a subgroup analysis showed that gains in axial stiffness varied in a dose-dependent fashion based on the total amount of exercise performed in the rowing-only arm. These findings were presented at the 2015 MHSRS and ASBMR. A manuscript is currently in preparation.

Key Research Accomplishments/Preliminary Findings to Date: We have several interim key research accomplishments based on analysis of baseline and 6 month data:

- Identification of adiponectin as a biomarker of lower extremity bone strength and fracture risk in motor complete SCI.

- Demonstration that FES-row training effectively circumvents the effect of the SCI on peak aerobic capacity by engaging more muscle mass for training, independent of level of injury.

-Finding that zoledronic acid mitigates lower extremity bone loss as effectively as FES-rowing.

-Finding that FES-rowing improves bone strength of the lower extremity in a dose dependent fashion.

Reportable Outcomes

Publications

Taylor JA, Picard G, Porter A, **Morse LR**, Pronovost M, Deley G. Hybrid FES exercise training alters the relationship between spinal cord injury level and aerobic capacity. Arch Phys Med Rehabil. 2014 Nov;95(11):2172-9.

Tan C, Battaglino R, Doherty A, Gupta R, Lazzari A, Garshick E, Zafonte R, **Morse LR.** Adiponectin is Associated with Bone Strength and Fracture History in Paralyzed Men with Spinal Cord Injury. Osteoporos Int. 2014 Nov;25(11):2599-607.

Awards

Best Paper Award, Fellow category, 2015 Annual meeting of Association of Academic Physiatrists (Saeed Alzahb, MD)

National and International Presentations

FES-Rowing Training Improves Bone Strength of the Paralyzed Legs in a Dose-Dependent Fashion. 2015 ASBMR (October, 2015).

FES-Rowing Training Improves Bone Strength of the Paralyzed Legs in a Dose-Dependent Fashion. 2015 MHSRS (August, 2015).

Exercise Program for Spinal Cord Injury Based on Hybrid Functional Electrical Stimulation Row Training, Oral Presentation, 62nd Annual ACSM Meeting, 6th World Congress on Exercise is Medicine® and World Congress on the Basic Science of Exercise Fatigue

Maximal Ventilation Limits Increased Aerobic Capacity with Hybrid Functional Electrical Stimulation Exercise Training in High Spinal Cord Injury, Oral presentation, 2015 Annual Association of Academic Physiatrists

Circulating Adiponectin Levels are Negatively Associated with Bone Strength in Males with Motor Complete SCI, Oral presentation, American Spinal Injury Association Annual Meeting, 2014

Bone Regenerative Effects of FES-Rowing, American Spinal Injury Association Annual Meeting, 2013

Effect of a Regular Rowing Exercise Program on Maximal Exercise Capacity in Spinal Cord Injury (SCI), Oral presentation, American Spinal Injury Association Annual Meeting, 2012

FES-rowing improves bone micro architecture and strength in the paralyzed lower extremity, Poster Presentation, 2012 Annual ISCoS meeting

Bone Regenerative Effects of FES-Rowing, Oral Presentation, First Annual Symposium on Regenerative Rehabilitation, McGowan Institute for Regenerative Medicine, University of Pittsburgh, 2011

Conclusion

We anticipate study completion December 2016. We have disseminated our work at national and international conferences with good reception and have published preliminary findings in 2 recent publications.

References
Not applicable

Appendices
None