Award Number: W81XWH-16-1-0763

BA150039

TITLE: Increasing Bone Mass and Bone Strength in Individuals with Chronic Spinal Cord Injury: Maximizing Response to Therapy

PRINCIPAL INVESTIGATOR: Thomas J. Schnitzer, MD, PhD

CONTRACTING ORGANIZATION: Northwestern University, Evanston, IL 60208

REPORT DATE: July 2019

TYPE OF REPORT: Final Report

PREPARED FOR: U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT:

☑ Approved for public release; distribution unlimited

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-

1. REPORT DATE *(DD-MM-YYYY)*	2. REPORT TYPE	3. DATES COVERED *(From - To)*
JULY 2019	Final Report	30 Sep 2016 - 29 MAR 2019

Increasing Bone Mass and Bone Strength in Individuals with Chronic Spinal Cord Injury: Maximizing Response to Therapy

5a. CONTRACT NUMBER
W81XWH-16-1-0763

5b. GRANT NUMBER
n/a

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
Thomas J. Schnitzer, MD, PhD

EMAIL: tjs@northwestern.edu

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Northwestern University, 633 Clark St., Evanston, IL 60208-0001

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

US Army Medical Research
Materiel Command
Fort Detrick, MD 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for public release; distribution unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

The overall objective of this research is to determine the optimal approach to enhancing and maintaining bone mass and bone strength in people with chronic SCI. Our previous research showed that teriparatide treatment results in an increase in bone mass in people with SCI. We hypothesized that initiating subsequent treatment with alendronate will further increase bone mass and bone strength. In this study, 17 participants recently completing teriparatide therapy were treated with open-label oral alendronate for one year and evaluated with bone imaging (DXA and CT scanning) and serum bone markers at 6 monthly intervals. Alendronate treatment prevented bone loss with significant increase in DXA BMD at the spine but not the hip; CT derived bone parameters increased at skeletal sites around the knee. FE modeling of cadaver specimens was able to predict stiffness and strength of both the proximal tibia and distal femur under complex biaxial loading, sufficient to stratify individuals into risk categories based on predicted strength or to assess longitudinal effects of intervention.

15. SUBJECT TERMS
Spinal cord injury, bone mass, bone strength, osteoporosis, alendronate, teriparatide

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
U	U	U	UU	26	19b. TELEPHONE NUMBER *(include area code)*

Table of Contents

Page

INTRODUCTION:

Spinal cord injury results in marked and rapid acute loss of bone which may be profound in magnitude, commonly being in the range of 15-30% at the hip and potentially even higher at sites of less weight-bearing and of greater trabecular content below the hip.[1-3] The clinical consequences of the decrease in both bone mass and bone quality in chronic SCI are reflected in a markedly increased rate of fracture, reported to be in the range of 1.2 to 3.4 per 100 patient years at risk.[4-6] This rate is similar to the rate of non-vertebral fractures occurring in post-menopausal osteoporotic women. Parathyroid hormone (PTH) is a potent bone-building hormone, and teriparatide (a biologic agent containing the amino-terminal 34 amino acids of human PTH) is the only anabolic agent approved by the FDA for the treatment of osteoporosis and the prevention of fractures.[7, 8] Although the optimal duration of teriparatide therapy for the treatment of osteoporosis is not known, discontinuation of teriparatide treatment has been shown to be followed by rapid decreases in bone mass and bone strength.[9, 10] These reductions in bone mass can be prevented by initiating treatment with a bone anti-resorptive agent once teriparatide is discontinued.[9-11] The current study takes advantage of a recently completed factorial designed clinical trial (NCT01225055)[12] of people with spinal cord injury (SCI) and low bone mass who have been treated with a combination of teriparatide and lower extremity loading (based on mechanical vibration) for either one or two years to determine if an additional year of alendronate treatment would prevent the expected bone loss with discontinuation of teriparatide.

OVERALL PROJECT SUMMARY:

The goal of the current study is to determine the effect of an additional year of treatment with the anti-resorptive agent, alendronate, a widely-used bisphosphonate, after discontinuation of teriparatide treatment for people with SCI and osteoporosis. The hypothesis being tested is that alendronate therapy will prevent the bone loss that occurs when teriparatide is stopped and possibly result in a further increase in bone mass and bone strength. In this study, participants completing the second year of the parent study with teriparatide were administered open-label oral alendronate 70mg weekly for 12 months. DXA imaging, CT imaging and bone markers were obtained at baseline, 6 months and 12 months to ascertain effects on bone mass, bone strength and bone metabolic processes. In addition, a parallel study using cadaveric bone specimens has been undertaken to evaluate and define parameters relating to bone strength to support a finite element analysis which will be used to define a fracture threshold which can be used to identify individuals who may be at high risk of bone failure and clinical fracture.

KEYWORDS: spinal cord injury, bone mass, bone strength, osteoporosis, alendronate, teriparatide

KEY RESEARCH ACCOMPLISHMENTS:

Specific Aims: (from SOW)

Specific Aim 1: Determine Effect of Treatment with alendronate on bone mass

Specific Aim 2: Determine Effect of Treatment with alendronate on bone strength

Specific Aim 3: Quantify changes in torsional and compressive strength at the distal femur and proximal tibia and correlate with fracture prevalence and incidence

AIMS 1 and 2:
Study Design:

This study was a single-site, non-randomized, open-label clinical trial conducted from April 2014 to August 2016 to determine if alendronate would be effective in maintaining the BMD increase observed after at least 12 months of teriparatide therapy. Invitation to enroll in this 12-month study was only offered to the group of participants with chronic SCI, who had recently completed a randomized controlled trial of teriparatide and/or vibration therapy (NCT01225055) and its open-label teriparatide extension (NCT02025179). These two teriparatide treatment clinical trials have been previously reported by our group[12] and hereafter, will be referred to as the parent protocol or parent study.

All visits occurred at Northwestern University Feinberg School of Medicine (NU) and the Rehabilitation Institute of Chicago (RIC), now known as the Shirley Ryan AbilityLab. Bone quality assessments were as described in the parent protocol. This study was registered with ClinicalTrials.gov (NCT02195895) and was approved by the Northwestern University Institutional Review Board (IRB) and DOD's Human Research Protection Office (HRPO). Informed consent was obtained prior to the start of any study procedures.

Results:

Participant Flow

Seventeen participants who completed the parent protocol agreed to participate and qualified to enroll in this open-label extension study. Thirteen participants completed the study per protocol. Four participants had to discontinue medication for varying lengths of time during the 12 months. One was on bed rest for a pressure sore, and unable to sit up for 30 minutes to safely take the drug. Two were taken off study drug due to a potential need for surgical tooth extraction, and one required fenestration of a spine syrinx (around week 24) and experienced medical complications. However, all returned for a final visit. Sixteen participants used the therapy for >76% of the 12-month duration of this study, while one used study drug for only 21% of the duration of this study. All participants were included in this report.

Table 1 Patient demographics and clinical descriptors

Open-label cohort, n	
Participants	17
Age, mean (SD)	
Years	44 (13)
Gender, n (%)	
Male	13 (76)
Female	4 (24)
Ethnicity, n (%)	
Non-Hispanic	14 (82)
Hispanic or Latino	3 (18)
Race, n (%)	
Caucasian	9 (53)
African-American	7 (41)
Asian	1 (6)
Time since injury, mean (SD)	
Years	15 (9)
Spine region, n (%)	
Cervical	4 (24)
Thoracic	11 (65)
Lumbar	2 (12)
AIS Classification, n (%)	
A	12 (71)
B	1 (6)
C	4 (24)
Injury severity, n (%)	
Motor complete tetraplegia (>T1)	3 (17)
Motor complete paraplegia (<C8)	10 (58)
Motor incomplete tetraplegia (>T1)	1 (6)
Motor incomplete paraplegia (<C8)	3 (18)
History of smoking, n (%)	
Yes	4 (23)
No	13 (75)
History of fracture after SCI, n (%)	
Prior to participation	5 (29)
During study	1 (5)
None	11 (65)
Hip aBMD at baseline, mean (SD)	
Z-Score	−2.5 (0.8)

Participant Demographic and Clinical Descriptors

As described in Table 1, the study population was predominantly male (76%). About half of the participants were Caucasian (53%) and just under half were African-American (41%). Thoracic level lesions were most common (65%), and approximately three-quarters of the patients were classified as American Spinal Injury Association Impairment Scale (AIS) A or B and had a motor complete injury. Four participants had a history of smoking. Finally, five participants had experienced at least one incident fracture after SCI and prior to the start of this study. One participant experienced a

fracture while in the study.

Effects of Alendronate on Bone Mass determined by DXA

As shown in Table 2 and Figure 1, 6 months of treatment with alendronate was not associated with a significant change to aBMD at the hip, femoral neck, or spine, with mean changes of 0.27% (95% CI, -1.7 to 2.2), 1.8% (95% CI, -1.0 to 4.6), and -1.6 (95% CI, -3.3 to 0.05), respectively. After 12 months of treatment, changes at the hip and femoral neck remained non-significant, with changes of 1.3% (95% CI, -1.1 to 3.8) and 0.54% (95% CI, -2.0 to 3.1), respectively. However, a significant increase in mean spine aBMD (2.5%; 95% CI, 0.17 to 4.9) was demonstrated after 12 months.

Effects of Alendronate on CT and FE Outcomes

As shown in Table 2 and Figure 1, we observed statistically significant improvements in a number of CT measures at the distal femur. After 6 months, cortical BMC increased by 14% (95% CI, 3.8 to 24) and cortical BV increased by 13% (95% CI, 4.0 to 23) at the epiphysis. Further improvements were seen after 12 months. At this time-point, cortical BMC increased by 15% (95% CI, 5.5 to 24), 7.7% (95% CI, 1.3 to 14) and 3.0% (95% CI, 1.2 to 4.8) at the epiphysis, metaphysis, and diaphysis, respectively. Similarly, there were also improvements to cortical BV at the epiphysis (15%; 95% CI, 5.8 to 23) and TSI of the metaphysis (4.6%; 95% CI, 1.1 to 8.2). However, a small decrease in diaphyseal cortical BV was also observed at 6 months (-4.3%; 95% CI, -5.6 to -3.0) and 12 months (-3.2%; 95% CI, -4.3 to -2.1).

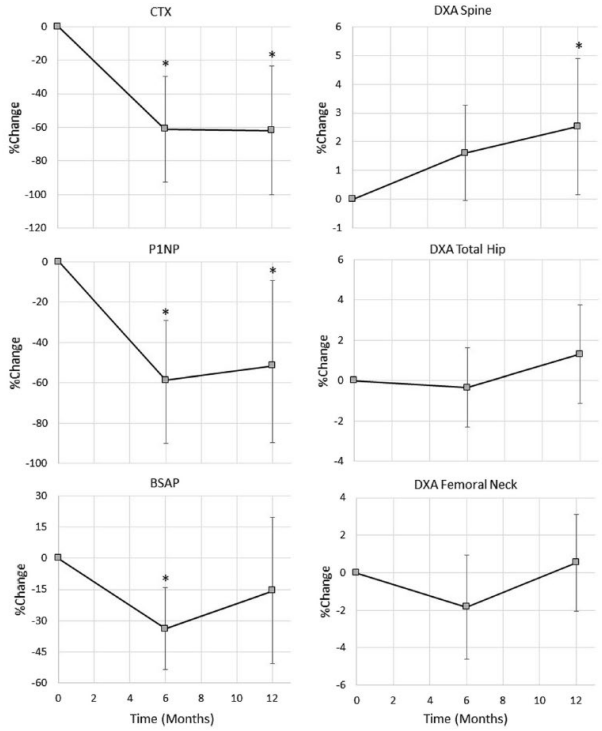

Fig. 1 Mean values (±95% confidence intervals) for serum biomarkers of bone metabolism (left) and select DXA measurements (right) relative to baseline

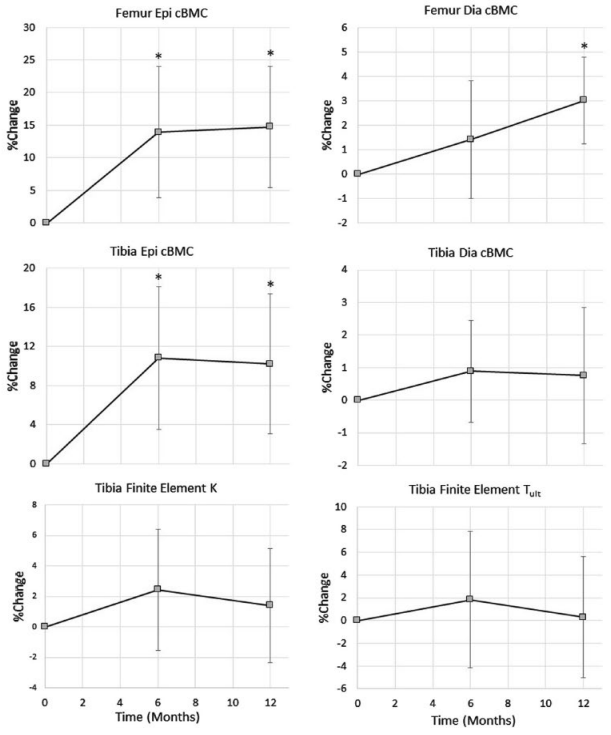

Fig. 2 Mean values (±95% confidence intervals) for select CT measurements at the distal femur (top), select CT measurements at the proximal tibia (middle), and finite element predictions of stiffness and strength (T_{ult}) at the proximal tibia (bottom)

Table 2 Results from baseline, 6 month and 12 month follow-up measurements

Measure		Baseline		6 Months		12 Months		% Change baseline vs 6 months		% Change baseline vs 12 months	
		n	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)	Mean difference (95% CI)	*p*-value	Mean difference (95% CI)	*p*-value
DXA	Spine [g/cm^2]	17	1.07 (0.131)	15	1.11 (0.111)	17	1.10 (0.156)	−1.61 (−3.27 to 0.05)	0.06	**2.54 (0.17 to 4.90)**	**0.04**
	Hip [g/cm^2]		0.596 (0.199)	14	0.588 (0.206)	16	0.604 (0.200)	0.27 (−1.70 to 2.23)	0.77	1.32 (−1.1 to 3.75)	0.27
	FN [g/cm^2]		0.615 (0.125)	15	0.604 (0.118)	17	0.619 (0.120)	1.82 (−1.00 to 4.60)	0.18	0.54 (−2.0 to 3.11)	0.66
FEMUR CT	Epi tBMD [g/cm^3]	17	0.051 (0.04)	14	0.05 (0.042)	17	0.049 (0.041)	1.76 (−6.68 to 10.2)	0.66	−4.28 (−11.8 to 3.19)	0.24
	Epi cBV [cm^3]		2.78 (1.611)		3.15 (1.71)		3.18 (1.63)	**13.2 (4.04 to 22.5)**	**0.01**	**14.5 (5.84 to 23.1)**	**0.00**
	Epi cBMC [g]		1.32 (0.802)		1.51 (0.844)		1.52 (0.82)	**13.9 (3.82 to 24.0)**	**0.01**	**14.7 (5.45 to 24.0)**	**0.00**
	Met tBMD [g/cm^3]		0.013 (0.052)		0.011 (0.041)		0.005 (0.037)	−26.6 (−119 to 66.2)	0.55	−63.2 (−162 to 35.7)	0.19
	Met cBV [cm^3]		10.3 (2.95)		10.0 (2.91)		10.4 (2.97)	1.49 (−7.68 to 10.7)	0.73	1.18 (−4.81 to 7.17)	0.68
	Met cBMC [g]		6.93 (2.54)		7.08 (2.52)		7.46 (2.66)	7.86 (−1.77 to 17.5)	0.10	**7.65 (1.31 to 14.0)**	**0.02**
	Met CSI [g^2/cm^4]		0.36 (0.211)		0.36 (0.215)		0.361 (0.210)	3.20 (−3.60 to 9.99)	0.33	0.16 (−8.40 to 8.72)	0.97
	Met TSI [cm^3]		1.44 (0.549)		1.44 (0.528)		1.50 (0.545)	4.12 (−0.39 to 8.63)	0.07	**4.63 (1.10 to 8.16)**	**0.01**
	Dia cBV [cm^3]		12.7 (2.85)		12.0 (2.93)		12.7 (2.85)	**−4.26 (−5.57 to −2.95)**	**0.00**	**−3.23 (−4.33 to −2.12)**	**0.00**
	Dia cBMC [g]		10.95 (3.33)		10.8 (3.41)		11.3 (3.31)	1.42 (−0.99 to 3.82)	0.23	**3.01 (1.23 to 4.80)**	**0.00**
TIBIA CT	Epi tBMD [g/cm^3]	17	0.031 (0.039)	14	0.033 (0.04)	17	0.029 (0.038)	7.33 (−3.25 to 17.9)	0.16	−4.53 (−12.6 to 3.58)	0.25
	Epi cBV [cm^3]		2.88 (1.21)		2.99 (1.20)		3.08 (1.20)	**7.56 (1.00 to 14.1)**	**0.03**	**7.00 (0.63 to 13.4)**	**0.03**
	Epi cBMC [g]		1.39 (0.643)		1.47 (0.620)		1.53 (0.643)	**10.8 (3.49 to 18.1)**	**0.01**	**10.2 (3.03 to 17.4)**	**0.01**
	Met tBMD [g/cm^3]		−0.002 (0.043)		0.001 (0.044)		−0.005 (0.044)	377 (−149 to 903)	0.15	**−127 (−219 to −33.8)**	**0.01**
	Met cBV [cm^3]		11.63 (3.10)		11.14 (3.03)		11.2 (2.86)	**−3.71 (−6.13 to −1.29)**	**0.01**	**−4.03 (−6.40 to −1.66)**	**0.00**
	Met cBMC [g]		8.23 (2.80)		8.30 (2.85)		8.36 (2.67)	1.87 (−0.68 to 4.42)	0.14	1.62 (−1.57 to 4.80)	0.30
	Met CSI [g^2/cm^4]		0.474 (0.257)		0.483 (0.270)		0.467 (0.257)	1.01 (−2.48 to 4.49)	0.54	−1.41 (−6.23 to 3.41)	0.54
	Met TSI [cm^3]		1.37 (0.443)		1.41 (0.468)		1.41 (0.440)	**3.35 (1.12 to 5.57)**	**0.01**	2.63 (−0.52 to 5.78)	0.10
	Dia cBV [cm^3]		13.9 (2.86)		13.3 (2.93)		13.4 (2.76)	**−3.40 (−4.72 to −2.08)**	**0.00**	**−3.70 (−5.20 to −2.21)**	**0.00**
	Dia cBMC [g]		11.9 (3.24)		11.8 (3.36)		12.0 (3.12)	0.88 (−0.68 to 2.45)	0.24	0.76 (−1.34 to 2.85)	0.46
FEM	*K* [N m/Degree]	17	17.3 (6.40)	14	17.3 (6.90)	17	17.5 (6.60)	2.40 (−1.54 to 6.40)	0.21	1.41 (−2.30 to 5.14)	0.43
	T_{ult} [N m]		50.8 (20.7)		51.2 (24.0)		51.0 (21.8)	1.80 (−4.17 to 7.80)	0.52	0.28 (−5.00 to 5.60)	0.91
Biomarkers	CTX [ng/mL]	17	0.217 (0.201)	15	0.092 (0.098)	17	0.083 (0.087)	**−60.9 (−92.4 to −29.4)**	**0.00**	**−61.8 (−99.8 to −23.7)**	**0.00**
	P1NP [ng/mL]		99.3 (47.7)		41.8 (24.6)		48.1 (57.7)	**−58.6 (−88.0 to −29.2)**	**0.00**	**−51.5 (−93.8 to −9.27)**	**0.02**
	BSAP [ng/mL]		11.4 (3.91)		7.57 (1.99)		9.65 (6.86)	**−33.9 (−53.5 to −14.2)**	**0.00**	−15.5 (−50.6 to 19.5)	0.36

Mean (SD) measurements across individuals are shown on the left. Mean percent difference (±95% confidence intervals) of follow-up visits compared to baseline are shown on the right. Significant differences from baseline are bolded

Epi epiphyseal, *Met* metaphyseal, *Dia* diaphyseal, *t* trabecular, *c* cortical

Improvements were somewhat diminished at the proximal tibia (Table 2). At this skeletal site we only observed increases in cortical BMC (10%; 95% CI, 3.0 to 17) and cortical BV (7%; 95% CI, 0.63 to 13) at the epiphysis after 12 months. However, cortical BV decreased in the metaphysis and diaphysis, with changes of -4.0% (95% CI, -6.4 to -1.7) and -3.7% (95% CI, -5.2 to -2.2), respectively. Similar changes in these measures were observed at the 6-month follow-up (Table 2), but we also observed that metaphyseal trabecular BMD decreased by -127% (95% CI, -219 to -34) after 12 months. However, even at baseline, trabecular BMD had a mean (SD) of -0.002 (0.043) g/cm3. The negative score here indicates that many individuals had little to no trabecular bone in this region even at the start of the study, and a reduction greater than 100% suggests a region that was entirely composed of marrow fat with little remaining hydroxyapatite after 12 months. No other changes were statically significant. We also did not observe statistically significant changes in FE-derived torsional stiffness ($p>0.21$) or strength ($p>0.52$) at the tibia at either the 6 or 12-month follow-up visits (Table 2 and Figure 2).

Biomarker Outcomes

Biomarker data were analyzed for all 17 participants. CTX, P1NP, and BSAP were all significantly lower after 6 months, with changes of -61% (95% CI, -92 to -29), -59% (95% CI, -88 to -29), and -34% (95% CI, -54 to -14), respectively. After 12 months, CTX remained 62% lower than baseline (95% CI, -100 to -24) and BSAP remained 52% lower than baseline (95% CI, -94 to -9.3), but changes to BSAP were no longer significant ($p=0.36$).

Safety Outcomes

Eighty-two percent of participants reported at least one adverse event during the course of the study. Eight of the adverse events reported were serious (bladder stone, inferior vena cava shift, two cases of sepsis secondary to an urinary tract infection (UTI), pressure sore, infection at the site of a pressure sore, spinal cord cysts, and two UTIs); however, none was felt to be related to study interventions.

Conclusions:

The results of this study indicate that one year of treatment with alendronate following discontinuation of treatment with teriparatide in people with SCI resulted in maintenance of bone mass at most skeletal sites. Alendronate therapy prevented the decrease in DXA-determined aBMD that has been reported to occur in able-bodied individuals after cessation of an anabolic intervention such as teriparatide therapy [19-21, 32, 33]. Not only did 12 months of alendronate therapy prevent bone loss, but a statistically significant increase in aBMD was observed at the spine and numerical increases in aBMD were demonstrated at the hip. Results were more variable at the distal femur and proximal tibia, the most common sites for fracture in this population. We observed increases in some skeletal parameters and bone strength indices at the distal femur, but with mixed results at the tibia.

AIM 3

Study Design:

Twenty-six cadaveric bones were obtained (mean age = 84.5 years; 14 tibia, 14 femur) from Science Care (Phoenix, AZ) as well as the University of Calgary Body Donation Program. Specimens were cleaned of soft tissue and osteotomy was performed 15 cm distal to the intercondylar eminence of the tibia or 15 cm proximal to the intercondylar fossa of the femur. The far-most 2 cm of the proximal and distal ends of the bones were fixed in polymethyl methacrylate (PMMA), leaving 11 cm of each bone exposed. Specimens were then imaged using quantitative computed tomography (QCT) on a GE Revolution GSI (GE Healthcare), with acquisition settings of 120 kVp, 500 mA, an in-plane resolution of 0.352 x 0. 352 mm, and slice thickness of 0.625 mm. After scanning, cadaveric specimens were mounted to a material testing machine (858 Mini Bionix II, MTS, Inc., Minneapolis, MN). Specimens were loaded in compression to 300 N (~50% bodyweight of an average individual) and held in displacement control. Torque (internal rotation) was then applied until specimen rupture or the 90 Nm safety limit of the load-cell was reached. The mechanical tests, which approximated the loading conditions of a fall from a wheelchair or a wheelchair transfer, were used to quantify torsional stiffness and multi-axial strength of each specimen.

Experimentally measured stiffness and strength was compared to predictions from subject-specific finite element (FE) models, generated from the QCT scans described above. The model was based on our previously FE modeling workflow, which was validated for the tibia in pure torsion only.[13] Images were down-sampled to a uniform 1.5mm voxel size, and a FE mesh was generated by simple voxel conversion. Loads and boundary conditions were applied to mimic the experimental protocol. Bone was modeled as a heterogeneous, orthotropic material. [13, 14]..Young's modulus in the axial direction was based on QCT derived measurement of bone density at each element location, using a relationship from literature.[15] Other elastic constants were derived from this value, using previously published ratios of anisotropy.[14] Bilinear material behavior was used to simulate failure; after yield, Young's Modulus was reduced to 5% of the pre-yield value. Yield was determined using Hill's conventional criterion, which has been shown to predict failure of bone under complex loading.[16] Finally, failure was defined as the torque, which caused 10% of surface elements to exceed a maximum principal strain of 1.41%,[13]

Results:

Experimental stiffness values were characterized for each specimen; however, experimental fracture strength could only be quantified for seven bones due to limits in our load cell. FE model predictions of torsional stiffness agreed with the experimental measurements (Fig 2; left), with a strong coefficient of determination (R^2 = 0.74) and a low average absolute error (15.8%). The average of the signed percent error was also only -3.1% suggesting that the model did not consistently over or underpredict stiffness. The FE model also accurately predicted fracture load for the seven bones that failed before the safe limit of 90 Nm (Fig 2; right). The average error was -34.7% demonstrating that the model consistently underpredict the measured fracture load. However, correlation between prediction and measurement was extremely strong (R^2 = 0.954). Finally, both stiffness and strength results were consistent across both tibiae and femura.

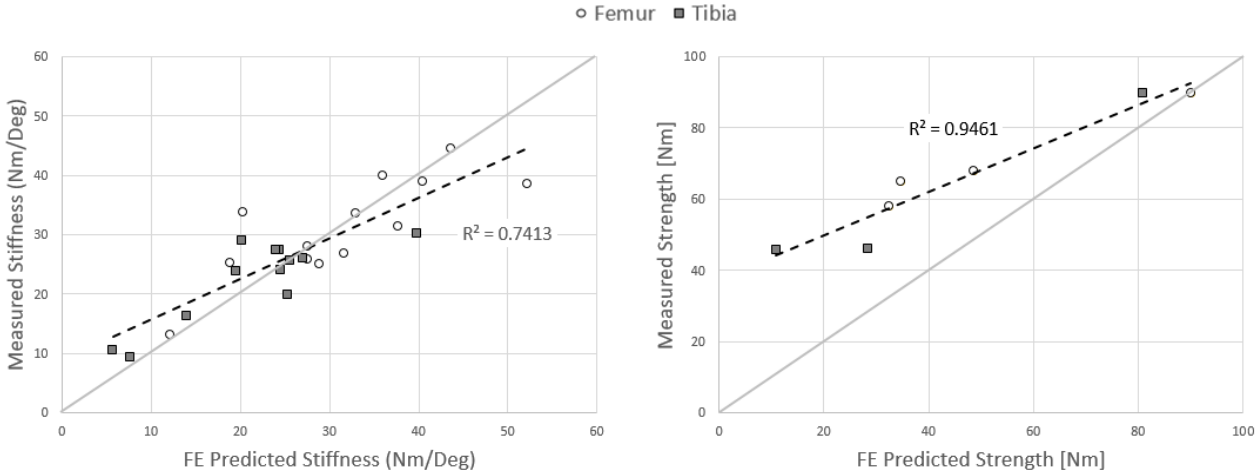

Figure 2: Experimental measures compared to FE predictions of torsional stiffness (LEFT) and strength (RIGHT). For both measures, we observed strong correlation between FE prediction and measurement (R^2 > 0.74). The line of unity, indicating zero error, is shown in gray.

Conclusions:

Results of this study indicate that the FE model is able to predict stiffness and strength of both the proximal tibia and distal femur under complex biaxial loading. This loading condition approximates that during a fall from a wheelchair or wheelchair transfer, and is likely highly clinically relevant. While the average error in fracture load was somewhat large, correlation between model predictions and experimental measurements remained extremely strong. This demonstrates that the model is able to identify relative differences in strength with little variance. As a result, we believe this model is sufficient to stratify individuals into risk categories based on predicted strength, or to assess longitudinal effects of intervention within individuals. This model is now being used to assess collected clinical data, in order to quantify the relationship between predicted strength and fracture risk in a clinical setting; these analyses are ongoing.

PUBLICATIONS, ABSTRACTS AND PRESENTATIONS:

Publications (to date):

1. Haider IT, Simonian N, Saini AS, Leung FM, Edwards WB, Schnitzer TJ. Open-label clinical trial of alendronate after teriparatide therapy in people with spinal cord injury and low bone mineral density. Spinal Cord. 2019 Jun 4. doi: 10.1038/s41393-019-0303-3. [Epub ahead of print] PMID: 31164732

Abstracts:

Haider IT, Lobos SM, Simonian N, Schnitzer TJ, Edwards WB. Finite Element Predicted Fracture Strength at Distal Femur and Proximal Tibia Under Biaxial Loading. *Podium Presentation at ISB/ASB 2019.* (International Society of Biomechanics/American Society of Biomechanics)

Presentations:

Haider IT, Lobos SM, Simonian N, Schnitzer TJ, Edwards WB. Finite Element Predicted Fracture Strength at Distal Femur and Proximal Tibia Under Biaxial Loading. *Podium Presentation at ISB/ASB 2019.* (International Society of Biomechanics/American Society of Biomechanics)

INVENTIONS, PATENTS AND LICENSES:

Nothing to report.

REPORTABLE OUTCOMES:

Nothing to report.

OTHER ACHIEVEMENTS:

Nothing to report.

REFERENCES:

1. Biering-Sorensen, F., H.H. Bohr, and O.P. Schaadt, *Longitudinal study of bone mineral content in the lumbar spine, the forearm and the lower extremities after spinal cord injury.* Eur J Clin Invest, 1990. **20**(3): p. 330-5.
2. Coupaud, S., et al., *Decreases in bone mineral density at cortical and trabecular sites in the tibia and femur during the first year of spinal cord injury.* Bone, 2015. **74**: p. 69-75.
3. Frey-Rindova, P., et al., *Bone mineral density in upper and lower extremities during 12 months after spinal cord injury measured by peripheral quantitative computed tomography.* Spinal Cord, 2000. **38**(1): p. 26-32.
4. Frisbie, J.H., *Fractures after myelopathy: the risk quantified.* J Spinal Cord Med, 1997. **20**(1): p. 66-9.
5. Lazo, M.G., et al., *Osteoporosis and risk of fracture in men with spinal cord injury.* Spinal Cord, 2001. **39**(4): p. 208-14.
6. Logan, W.C., Jr., et al., *Incidence of fractures in a cohort of veterans with chronic multiple sclerosis or traumatic spinal cord injury.* Arch Phys Med Rehabil, 2008. **89**(2): p. 237-43.
7. Finkelstein, J.S., et al., *The effects of parathyroid hormone, alendronate, or both in men with osteoporosis.* N Engl J Med, 2003. **349**(13): p. 1216-26.
8. Neer, R.M., et al., *Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis.* N Engl J Med, 2001. **344**(19): p. 1434-41.
9. Lindsay, R., et al., *Sustained Vertebral Fracture Risk Reduction After Withdrawal of Teriparatide in Postmenopausal Women With Osteoporosis.* Arch Intern Med, 2004. **164**: p. 2024-2030.
10. Black, D.M., et al., *One year of alendronate after one year of parathyroid hormone (1-84) for osteoporosis.* N Engl J Med, 2005. **353**(6): p. 555-65.
11. Cosman, F., et al., *Parathyroid hormone added to established hormone therapy: effects on vertebral fracture and maintenance of bone mass after parathyroid hormone withdrawal.* J Bone Miner Res, 2001. **16**(5): p. 925-31.
12. Edwards, W.B., et al., *Effects of Teriparatide and Vibration on Bone Mass and Bone Strength in People with Bone Loss and Spinal Cord Injury: A Randomized, Controlled Trial.* J Bone Miner Res, 2018. **33**(10): p. 1729-1740.
13. Edwards, W.B., T.J. Schnitzer, and K.L. Troy, *Torsional stiffness and strength of the proximal tibia are better predicted by finite element models than DXA or QCT.* Journal of Biomechanics, 2013. **46**(10): p. 1655-62.
14. Rho, J.Y., *An ultrasonic method for measuring the elastic properties of human tibial cortical and cancellous bone.* Ultrasonics, 1996. **34**(8): p. 777-83.
15. Rho, J.Y., M.C. Hobatho, and R.B. Ashman, *Relations of mechanical properties to density and CT numbers in human bone.* Med Eng Phys, 1995. **17**(5): p. 347-55.
16. Cezayirlioglu, H., et al., *Anisotropic yield behavior of bone under combined axial force and torque.* J Biomech, 1985. **18**(1): p. 61-9.

APPENDICES:

Appendix A. List of personnel receiving salary

Appendix B. Methodology for DXA and CT acquisition and analysis and quantitation of bone markers

Appendix C. Copies of abstracts and publications

Appendix A: Personnel Receiving Salary

Name	Title
Gregory, Elaine	Post-doctoral fellow; clinician
Haider, Ifaz	Post-doctoral fellow; Calgary
Nigg, Narina Simonian	Research Project Manager
Saini, Aman	Post-doctoral fellow; clinician
Schnitzer, Thomas	Principal Investigator

Appendix B. Methodology for DXA and CT acquisition and analysis and quantitation of bone markers

DXA Acquisition and Analysis

The DXA scans were performed using a Hologic QDR 4500A (Hologic, Waltham, MA, USA); standard acquisition and analysis protocols were used to quantify areal bone mineral density (aBMD) of spine, femoral neck and total proximal femur regions bilaterally.(1) For knee aBMD acquisition, a modified forearm algorithm was elected for scan acquisition, with the imaging field comprising the distal 2/3 of the femur and the proximal 1/3 of the tibia. The distal femur was divided into 2 regions for analysis, the femoral epiphysis (R1) and the metaphysis (R2) with a separate region of interest for the proximal tibia (R3) as described in a previous publication.(2) During scans, participants were placed in a supine position and the lower limb was stabilized in full extension. When possible, duplicate scans were obtained. We performed calibrations of the machine prior to each subject visit using a spine phantom, air scans and tissue bar scans. The day-to-day coefficient of variation (CV) of the spine phantom over the testing period was 0.387% (n=315). The precision of the DXA measurements at the distal femur epiphysis, distal femur metaphysis and the proximal tibia has been previously published, with the root-mean-square (RMS) CV being 3.12%, 4.70% and 3.40%, respectively.(3) If heterotopic ossification was visualized within the region of interest, data from that skeletal site was not utilized. Similarly, regions of interest containing metallic objects were also excluded.

CT Acquisition

Computed tomography data were acquired for the non-dominant knee (i.e., contralateral to hand dominance) of each participant using a scan length that captured the proximal most 15 cm of the tibia. The CT scans were performed using a Sensation 64 Cardiac Scanner (Siemens Medical Systems, Forchheim, Germany) with acquisition settings of 120 kVp and 200 mAs. Images were reconstructed with a slice thickness of 1 mm and an in-plane pixel resolution of 0.352 mm. All scans included a phantom in the field of view with known calcium hydroxyapatite concentrations (QRM, Moehrendorf, Germany).

QCT mineral analysis

QCT mineral analysis of the proximal tibia was performed using established protocols. (2, 4) Briefly, CT data were imported to Mimics (Materialise, Leuven, Belgium) where images were re-aligned so that the axial direction corresponded to the long axis of the tibia; the mediolateral axis was defined by a line passing through the medial and lateral condyles of the tibia and the anterioposterior axis was oriented orthogonally. The CT Hounsfield units were converted to calcium hydroxyapatite density ρ_{ha} using a linear relationship established with the phantom. This process can result in negative ρ_{ha} values for voxels comprised primarily of marrow fat.(5)

Proximal tibiae were segmented from the aligned images using a ρ_{ha} threshold of 0.15 g/cm3 to identify the periosteal surface boundary. Integral volumetric bone mineral density (vBMD; g/cm3) and bone mineral content (BMC; g) were calculated for the total proximal tibia, defined as all voxels within the periosteal surface boundary. The total proximal tibia included the first 30% of segment length, as measured from the proximal end of the bone. Segment lengths were estimated from self-reported stature using the proportionality constants of Drillis and Contini as cited by Winter.(6)

Local measures of compartmental bone were computed for epiphyseal, metaphyseal, and diaphyseal regions of the proximal tibia corresponding to 0-10%, 10-20%, and 20-30% of segment length, respectively. Cortical and trabecular compartments were identified as previously described [Edwards et al., 2013; 2014].(2, 4) Local measures of cortical vBMD and BMC were computed for the epiphysis,

metaphysis and diaphysis. Local measures of trabecular vBMD and BMC were only computed for the epiphysis and metaphysis. In addition, integral and cortical bone volumes (BV; cm3) were quantified for each region and used as surrogate measures of periosteal and endosteal expansion, respectively.

Bone Markers

Serum was obtained at baseline and each subsequent visit and frozen at -70C until assessed for type 1 procollagen amino-terminal propeptide (P1NP), collagen type 1 cross-linked C-telopeptide (CTX) and bone-specific alkaline phosphatase (BSAP) by Maine Medical Research Institute, Scarborough, ME, utilizing iSIS Analyzer (Luminescence) system, Immunodiagnostic Systems, Inc, Scottsdale, AZ.

1. Gordon KE, Wald MJ, Schnitzer TJ. Effect of parathyroid hormone combined with gait training on bone density and bone architecture in people with chronic spinal cord injury. Pm R. 2013;5(8):663-71. Epub 2013/04/06.
2. Edwards WB, Schnitzer TJ, Troy KL. Bone mineral and stiffness loss at the distal femur and proximal tibia in acute spinal cord injury. Osteoporos Int. 2014;25(3):1005-15. Epub 2013/11/06.
3. McPherson JG, Edwards WB, Prasad A, Troy KL, Griffith JW, Schnitzer TJ. Dual energy X-ray absorptiometry of the knee in spinal cord injury: methodology and correlation with quantitative computed tomography. Spinal Cord. 2014;52(11):821-5. Epub 2014/07/16.
4. Edwards WB, Schnitzer TJ, Troy KL. Torsional stiffness and strength of the proximal tibia are better predicted by finite element models than DXA or QCT. J Biomech. 2013;46(10):1655-62. Epub 2013/05/18.
5. Marshall LM, Lang TF, Lambert LC, Zmuda JM, Ensrud KE, Orwoll ES. Dimensions and volumetric BMD of the proximal femur and their relation to age among older U.S. men. J Bone Miner Res. 2006;21(8):1197-206. Epub 2006/07/28.
6. Winter DA. Biomechanics and motor control of human movement. 2nd ed. New York: John Wiley & Sons, Inc.; 1990.

Spinal Cord
https://doi.org/10.1038/s41393-019-0303-3

ARTICLE

Open-label clinical trial of alendronate after teriparatide therapy in people with spinal cord injury and low bone mineral density

Ifaz T. Haider[1,2] · Narina Simonian[3,4] · Amanpreet S. Saini[3] · Frances M. Leung[3] · W. Brent Edwards[1,2] · Thomas J. Schnitzer[3]

Received: 3 February 2019 / Revised: 6 May 2019 / Accepted: 7 May 2019

Abstract

Study design Non-randomized open-label clinical trial of oral alendronate after teriparatide therapy in people with spinal cord injury (SCI) and low bone mineral density (BMD).

Objectives To determine if alendronate would prevent bone loss after discontinuation of teriparatide.

Setting Outpatient research clinic at Northwestern University Feinberg School of Medicine.

Methods Seventeen participants with chronic SCI who recently completed 12–24 months of teriparatide treatment received oral alendronate 70 mg once weekly for 12 months. Participants were evaluated at baseline, 6 months and 12 months. Bone was assessed by: DXA at the spine and hip, CT at the distal femur/proximal tibia, serum collected for bone markers, and bone strength determined by finite element (FE) analysis of the proximal tibia.

Results Areal BMD showed no significant change from baseline at the total hip or femoral neck, where mean change (SD) was 1.3% (4.7) and 0.54% (5.0), respectively. However, areal BMD increased significantly at the spine by 2.5% (4.6). CT demonstrated significant increases in bone mineral content at the femoral epiphysis, metaphysis, and diaphysis, 15% (18), 7.7% (12), and 3.0% (3.5), respectively. Measurements at the tibia illustrated improvements and reductions, but no changes to FE-predicted strength were observed. Biomarkers illustrated inhibition of bone formation and resorption, with P1NP and CTX decreasing by 52% (82) and 62% (74), respectively.

Conclusion Twelve months of alendronate after discontinuation of teriparatide in people with SCI can prevent bone loss and may increase bone mass and preserve bone strength at the spine, hip, and some sites of the knee.

Introduction

Many individuals with acute spinal cord injury (SCI) experience a significant reduction (up to 60%) of bone mass and bone strength in their femur and tibia with bone loss being most rapid in magnitude during the first 1–3 years after injury [1–3]; thereafter, the rate of bone loss slows, reaching a new steady state [4, 5]. The rapid demineralization in the acute SCI setting stems primarily from the cessation of weight-bearing [6], which accompanies motor complete and many motor incomplete injuries [7]. By the time the injury reaches a chronic stage, the amount of bone mass remaining is low, making the bone weak and highly susceptible to fractures [8]. Fracture incidence in people with SCI increases with injury duration, with mean time to first fracture reported to be 6–9 years after SCI [9, 10]. Fractures occur predominantly below the neurological level of the SCI lesion, most commonly occurring in the lower extremities, where bone loss and changes to bone microarchitecture are most significant [9, 11, 12]. These fractures are often a consequence of minimal to no trauma and can lead to secondary complications [12–14], further loss of independence, increased financial burden, and the likelihood of another fracture [15].

✉ Thomas J. Schnitzer
tjs@northwestern.edu

1 Human Performance Laboratory, Faculty of Kinesiology, University of Calgary, Calgary, AB T2N 1N4, Canada

2 McCaig Institute for Bone and Joint Health, University of Calgary, Calgary, AB T2N 1N4, Canada

3 Department of Physical Medicine and Rehabilitation, Northwestern University Feinberg School of Medicine, Chicago, IL 60611, USA

4 Northwestern University Clinical and Translational Sciences Institute, Northwestern University Feinberg School of Medicine, Chicago, IL 60611, USA

Published online: 04 June 2019

Currently, there is no standard of care to treat the existing bone loss and the high risk of fracture in the chronic SCI population. Rebuilding lost bone mass would be an important step in the reduction of fracture incidence. Therefore, treatment with anabolic agents, which increase bone strength and decrease fracture incidence by stimulating bone formation, would be the expected approach [16, 17]. Our group has recently reported on the use of teriparatide [18], a peptide containing the biologically active N-terminal 34 amino acids of parathyroid hormone and the only anabolic bone agent available at the time the study was started, in people with chronic SCI. In that clinical trial, though treatment with teriparatide was not associated with robust improvements in bone mineral density (BMD) at the knee, treatment did result in modest increases in BMD at the spine and hip in people with long-standing SCI after 1 or 2 years of treatment.

Termination of teriparatide therapy without initiating further pharmacologic intervention is known to lead to rapid loss of the newly gained bone [19–22]. Treatment with alendronate after at least a year of teriparatide therapy has been demonstrated to prevent such bone loss and either maintain or further increase bone mass [19, 22]. Based on these observations, the current study was undertaken to examine the effects of bisphosphonate treatment (1 year of alendronate) on bone mass and bone quality in patients with chronic SCI after the discontinuation of anabolic therapy (1 or 2 years with teriparatide). We expected to observe either maintenance or increase in bone measures, over the course of the study.

Methods

Study design

This study was a single-site, non-randomized, open-label clinical trial conducted from April 2014 to August 2016 to determine if alendronate would be effective in maintaining the BMD increase observed after at least 12 months of teriparatide therapy. Invitation to enroll in this 12-month study was only offered to the group of participants with chronic SCI, who had recently completed a randomized controlled trial of teriparatide and/or vibration therapy (NCT01225055) and its open-label teriparatide extension (NCT02025179). These two teriparatide treatment clinical trials have been previously reported by our group [18] and hereafter, will be referred to as the parent protocol or parent study.

All visits occurred at Northwestern University Feinberg School of Medicine (NU) and the Rehabilitation Institute of Chicago (RIC), now known as the Shirley Ryan AbilityLab. Bone quality assessments mirrored those of the lead site as described in the parent protocol [18]. This study was registered with ClinicalTrials.gov (NCT02195895) and was approved by the Northwestern University Institutional Review Board (IRB) and DOD's Human Research Protection Office (HRPO). Informed consent was obtained prior to the start of any study procedures.

Study participants

To be eligible for the parent protocol [18], participants (male or female) were required to be at least 21 years old, and non-ambulatory following a history of SCI, classified based on chart review or assessment by the referring physician. They were also required to have (1) low bone mass at the total hip or femoral neck based on dual-energy absorptiometry (DXA), with a Z-score ≤ -1.5, T-score ≤ -2.5, or T-score < -2.0 with a history of a fragility fracture, (2) a SCI at least 1 year before the start of the study, (3) an ASIA impairment score of A, B, C, or D (non-ambulatory), (4) normal renal function, TSH, and calcium levels, and (5) 25-OH Vitamin D levels ≥20 ng/ml at baseline. Individuals were excluded if they (1) had known allergies to teriparatide or a history of teriparatide use (last 24 months), (2) had a history of bone metastasis, radiation therapy, or Paget's disease of bone, (3) used anticonvulsants at a frequency determined to interfere with bone metabolism, (4) had elevated liver function (more than two times normal limit), and (5) were pregnant, lactating, or planning on becoming pregnant.

Out of the 24 individuals who completed the parent protocol and received 1 or 2 years of teriparatide therapy, 17 agreed to participate in the current study. Of the seven who did not continue, only one cited a medically relevant reason, as they were not able to sit up for 30 min to safely take the drug.

Study treatment and procedures

Each participant from the parent protocol was further screened to ensure safety prior to enrolling in this open-label study. Major exclusion criteria included: (1) renal insufficiency, (2) not able to sit upright for at least 30 min after taking study medication, (3) poor dental hygiene or plans for dental surgery in the next year, and (4) esophageal abnormalities.

After passing the screening procedures, participants were carefully instructed in the proper way to take the study drug (first thing in the morning, sitting upright, on an empty stomach with a full glass of water, etc.). Participants received study drug (alendronate 70 mg) for weekly use and supplemental vitamin D (cholecalciferol 1000 IU) and calcium (calcium carbonate 1000 mg) for daily use. Study drug and supplements were provided in sufficient quantities to last until the next clinic visit. Follow-up study visits

occurred every 3 months after the initiation of study treatment over the course of 12 months. Adverse events and compliance were assessed at each visit.

Bone quality assessments were collected at baseline, and again at 6 and 12 month after starting alendronate therapy, and included DXA scans of the lumbar spine and bilateral hips, computed tomography (CT) of the non-dominant knee, and serum bone markers (collagen type 1 cross-linked C-telopeptide [CTX], type 1 procollagen amino-terminal propeptide [P1NP], and bone-specific alkaline phosphatase [BSAP]). Since enrollment into this study began shortly after the completion of the parent protocol and the bone quality assessments were identical in all studies, the final (month 24) visit of the parent protocol was used as the baseline visit for this study. If more than 3 months elapsed between the studies, bone serum markers, DXA and CT imaging were repeated prior to the start of study treatment.

DXA acquisition and analysis

All scans were performed with a Hologic QDR 4500A (Hologic, Waltham, MA, USA) as previously described [23]. Standard acquisition and analysis protocols were used to quantify areal BMD (aBMD) of the lumbar spine, total hip and femoral neck, from frontal plane images. Quality control of the DXA machine included measurements of the spine phantom daily, body phantom three times/week, and air scan and tissue bar scans weekly. The non-dominant hip data (total hip and femoral neck) were chosen for analysis. For participants with significant heterotopic ossification (HO) or other artifacts in the region of interest, the dominant hip data were used.

CT acquisition and analysis

CT image acquisition and analysis were performed according to a previously published protocol [18], repeated here briefly. Scans of the knee were acquired using a Sensation 64 Cardiac Scanner (Siemens Medical Systems, Forchheim, Germany), with scan settings of 120 kVp and 280 mA. Images were acquired with an in-plane resolution of 0.352×0.352 mm with a 1 mm slice spacing. A 30 cm long scan was used to capture ~15 cm of the proximal tibia and distal femur, respectively. A hydroxyapatite calibration phantom was placed in the field-of-view, which allowed us to identify a linear regression relationship between mineral density (g/cm^3) and CT absorption (HU; Hounsfield units).

Regions of interest from each scan were identified using Mimics (Materialise, Leuven, Belgium) software. A threshold of 0.15 g/cm^3 was used to identify the periosteal surface of the bone, and some manual clean-up was done to isolate each bone and fill in small gaps at the epiphysis. Images from the baseline assessment, prior to any treatment, were manually aligned along the longitudinal axes of the tibia and femur. Scans from each follow-up visit were registered to their corresponding aligned baseline images using a least-squares optimization algorithm available in the Mimics software.

Aligned scans of each bone were separated into different regions for CT analysis. First, segment lengths (SL) were estimated from published proportionality constants [24] and self-reported stature. Segment lengths were then used to separate each bone into epiphyseal (0–10% SL), metaphyseal (10–20% SL), and diaphyseal (20–30% SL) regions. Each region was further separated into integral, trabecular, and cortical compartments. The integral compartment contained all voxels within the periosteal surface. The trabecular compartment was identified by applying a 10-pixel (3.52 mm) in-plane erosion to the integral compartment. Finally, cortical bone was identified by Boolean subtraction of the trabecular region from the integral region, followed by a thresholding of 0.35 g/cm^3 to remove any remaining trabecular bone. We reported volumetric bone mineral density (vBMD; g/cm^3) for trabecular bone and bone mineral content (BMC; g) and bone volume (BV; cm^3) for cortical bone. The trabecular compartment was omitted from analysis of the diaphyseal region. Finally, we computed a compressive strength index (CSI; g^2/cm^4) and torsional strength index (TSI; cm^3) using previously reported equations [25, 26].

Finite element analysis

We also generated CT-based, subject-specific finite element (FE) models of each bone, in order to assess torsional stiffness and strength. Briefly, images were resampled to isotropic 1.5 mm resolution voxels and a hexahedral mesh of the same size was generated by voxel conversion. Material properties were assigned based on average CT intensity at each element location using equation 1:

$$E_3 = 6570 \cdot \rho_{app}^{1.37} \quad (1)$$

$$\rho_{app} = \frac{\rho_{HU}}{0.626} \quad (1a)$$

where E_3 is the Young's modulus in the proximal–distal direction (MPa), ρ_{app} is the apparent density (g/cm^3) and ρ_{HU} is the CT-derived density (g/cm^3). The other elastic constants were computed using previously published ratios of anisotropy: $E_1 = 0.574 \cdot E_3$, $E_2 = 0.577 \cdot E_3$, $G_{12} = 0.195 \cdot E_3$, $G_{23} = 0.265 \cdot E_3$, $G_{31} = 0.216 \cdot E_3$, $\nu_{12} = 0.427$, $\nu_{23} = 0.234$, and $\nu_{31} = 0.405$ [27]. Here subscripts 1, 2, and 3 denote the medial–lateral, anterior–posterior, and proximal–distal directions, respectively. Bone material failure was simulated using a bilinear elastic-plastic model, where yield was defined with a quadratic Hill criterion for

orthotropic materials [28]. Surface nodes on 2 cm of the diaphyseal end were rigidly fixed, while torsional displacement was applied to surface nodes on 2 cm of the epiphyseal end. Torsional stiffness (K_t) was quantified from the linear region of the simulated torque-rotation response. Torsional strength (T_{ult}) was computed as the applied torque required to cause 10% of the surface to exceed a maximum principle strain of 1.41% [29]. This modeling procedure was thoroughly validated using cadaveric tibiae [29], and has been used to study individuals with SCI [18, 30, 31].

Statistical analysis

Statistical analyses were performed using SPSS software (version 24, IBM, NY, USA). The primary outcome measure was percent change in DXA BMD at the total hip at 12 months. Secondary outcome measures included changes in BMD at other skeletal sites, changes in CT-defined skeletal outcome measures and serum biomarker changes. Paired Student's *t*-tests were performed at a significance level of 0.05, comparing the value of each measure at follow-up against the baseline measured prior to treatment with alendronate. To confirm validity of this test, we assessed the normality of paired differences using the Shapiro-Wilks tests evaluated at a significance level of 0.05.

Results

Participant flow

Seventeen participants who completed the parent protocol agreed to participate and qualified to enroll in this open-label extension study. Thirteen participants completed the study per protocol. Four participants had to discontinue medication for varying lengths of time during the 12 months. One was on bed rest for a pressure sore, and unable to sit up for 30 min to safely take the drug. Two were taken off study drug due to a potential need for surgical tooth extraction, and one required fenestration of a spine syrinx (around week 24) and experienced medical complications. However, all returned for a final visit. Sixteen participants used the therapy for >76% of the 12-month duration of this study, while one used study drug for only 21% of the duration of this study. This individual was assessed as a possible outlier, but excluding their data did not have a meaningful impact on the significance of the results. Thus, all participants were included in this report.

Participant demographic and clinical descriptors

As described in Table 1, the study population was predominantly male (76%). About half of the participants were Caucasian (53%) and just under half were African-American (41%). Thoracic level lesions were most common (65%), and approximately three-quarters of the patients were classified as American Spinal Injury Association Impairment Scale (AIS) A or B and had a motor complete injury. Four participants had a history of smoking. Finally, five participants had experienced at least one incident fracture after SCI and prior to the start of this study. One participant experienced a fracture while in the study; this individual was also assessed as a possible outlier. Excluding

Table 1 Patient demographics and clinical descriptors

Open-label cohort, n	
Participants	17
Age, mean (SD)	
Years	44 (13)
Gender, n (%)	
Male	13 (76)
Female	4 (24)
Ethnicity, n (%)	
Non-Hispanic	14 (82)
Hispanic or Latino	3 (18)
Race, n (%)	
Caucasian	9 (53)
African-American	7 (41)
Asian	1 (6)
Time since injury, mean (SD)	
Years	15 (9)
Spine region, n (%)	
Cervical	4 (24)
Thoracic	11 (65)
Lumbar	2 (12)
AIS Classification, n (%)	
A	12 (71)
B	1 (6)
C	4 (24)
Injury severity, n (%)	
Motor complete tetraplegia (>T1)	3 (17)
Motor complete paraplegia (<C8)	10 (58)
Motor incomplete tetraplegia (>T1)	1 (6)
Motor incomplete paraplegia (<C8)	3 (18)
History of smoking, n (%)	
Yes	4 (23)
No	13 (75)
History of fracture after SCI, n (%)	
Prior to participation	5 (29)
During study	1 (5)
None	11 (65)
Hip aBMD at baseline, mean (SD)	
Z-Score	−2.5 (0.8)

their data had little impact on the significance of our results, and so all data were kept in the final analysis.

DXA outcomes

DXA measurements were analyzed for all 17 participants, with the exception of one individual's total hip being omitted due to HO. As shown in Table 2 and Fig. 1, 6 months of treatment with alendronate was not associated with a significant change to aBMD at the hip, femoral neck, or spine, with mean changes of 0.27% (95% CI, −1.7 to 2.2), 1.8% (95% CI, −1.0 to 4.6), and −1.6 (95% CI, −3.3 to 0.05), respectively. After 12 months of treatment, changes at the hip and femoral neck remained non-significant, with changes of 1.3% (95% CI, −1.1 to 3.8) and 0.54% (95% CI, −2.0 to 3.1), respectively. However, a significant increase in mean spine aBMD (2.5%; 95% CI, 0.17 to 4.9) was demonstrated after 12 months.

CT and FE outcomes

As shown in Table 2 and Fig. 1, we observed statistically significant improvements in a number of CT measures at the distal femur. After 6 months, cortical BMC increased by 14% (95% CI, 3.8 to 24) and cortical BV increased by 13% (95% CI, 4.0 to 23) at the epiphysis. Further improvements were seen after 12 months. At this time-point, cortical BMC increased by 15% (95% CI, 5.5 to 24), 7.7% (95% CI, 1.3 to 14), and 3.0% (95% CI, 1.2 to 4.8) at the epiphysis, metaphysis, and diaphysis, respectively. Similarly, there were also improvements to cortical BV at the epiphysis (15%; 95% CI, 5.8 to 23) and TSI of the metaphysis (4.6%; 95% CI, 1.1 to 8.2). However, a small decrease in diaphyseal cortical BV was also observed at 6 months (−4.3%; 95% CI, −5.6 to −3.0) and 12 months (−3.2%; 95% CI, −4.3 to −2.1).

Improvements were somewhat diminished at the proximal tibia (Table 2). At this skeletal site we only observed increases in cortical BMC (10%; 95% CI, 3.0 to 17) and cortical BV (7%; 95% CI, 0.63 to 13) at the epiphysis after 12 months. However, cortical BV decreased in the metaphysis and diaphysis, with changes of −4.0% (95% CI, −6.4 to −1.7) and −3.7% (95% CI, −5.2 to −2.2), respectively. Similar changes in these measures were observed at the 6-month follow-up (Table 2), but we also observed that metaphyseal trabecular BMD decreased by −127% (95% CI, −219 to −34) after 12 months. However, even at baseline, trabecular BMD had a mean (SD) of −0.002 (0.043) g/cm^3. The negative score here indicates that many individuals had little to no trabecular bone in this region even at the start of the study, and a reduction >100% suggests a region that was entirely composed of marrow fat with little remaining hydroxyapatite after 12 months. No other changes were statically significant. We also did not observe statistically significant changes in FE-derived torsional stiffness ($p > 0.21$) or strength ($p > 0.52$) at the tibia at either the 6 or 12-month follow-up visits (Table 2 and Fig. 2).

Biomarker outcomes

Biomarker data were analyzed for all 17 participants. CTX, P1NP, and BSAP were all significantly lower after 6 months, with changes of −61% (95% CI, −92 to −29), −59% (95% CI, −88 to −29), and −34% (95% CI, −54 to −14), respectively. After 12 months, CTX remained 62% lower than baseline (95% CI, −100 to −24) and BSAP remained 52% lower than baseline (95% CI, −94 to −9.3), but changes to BSAP were no longer significant ($p = 0.36$).

Safety outcomes

Eighty-two percent of participants reported at least one adverse event during the course of the study. Eight of the adverse events reported were serious (bladder stone, inferior vena cava shift, two cases of sepsis secondary to an urinary tract infection (UTI), pressure sore, infection at the site of a pressure sore, spinal cord cysts, and two UTIs); however, none was felt to be related to study interventions.

Discussion

The results of this study indicate that one year of treatment with alendronate following discontinuation of treatment with teriparatide in people with SCI resulted in maintenance of bone mass at most skeletal sites. Alendronate therapy prevented the decrease in DXA-determined aBMD that has been reported to occur in able-bodied individuals after cessation of an anabolic intervention such as teriparatide therapy [19–21, 32, 33]. Not only did 12 months of alendronate therapy prevent bone loss, but a statistically significant increase in aBMD was observed at the spine and numerical increases in aBMD were demonstrated at the hip. However, these are less common sites of fracture in individuals with SCI, therefore these changes may not be clinically meaningful. Results were more variable at the distal femur and proximal tibia, the most common sites for fracture in this population. We observed increases in some skeletal parameters and bone strength indices at the distal femur, but with mixed results at the tibia.

Until recently, teriparatide has been the only anabolic agent approved to treat osteoporosis in post-menopausal women and older, osteoporotic men [32, 33]. An additional anabolic agent, abaloparatide, a parathyroid-related protein

Table 2 Results from baseline, 6 month and 12 month follow-up measurements

Measure		Baseline		6 Months		12 Months		% Change baseline vs 6 months		% Change baseline vs 12 months	
		n	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)	Mean difference (95% CI)	*p*-value	Mean difference (95% CI)	*p*-value
DXA	Spine [g/cm^2]	17	1.07 (0.131)	15	1.11 (0.111)	17	1.10 (0.156)	−1.61 (−3.27 to 0.05)	0.06	**2.54 (0.17 to 4.90)**	**0.04**
	Hip [g/cm^2]		0.596 (0.199)	14	0.588 (0.206)	16	0.604 (0.200)	0.27 (−1.70 to 2.23)	0.77	1.32 (−1.1 to 3.75)	0.27
	FN [g/cm^2]		0.615 (0.125)	15	0.604 (0.118)	17	0.619 (0.120)	1.82 (−1.00 to 4.60)	0.18	0.54 (−2.0 to 3.11)	0.66
FEMUR CT	Epi tBMD [g/cm^3]	17	0.051 (0.04)	14	0.05 (0.042)	17	0.049 (0.041)	1.76 (−6.68 to 10.2)	0.66	−4.28 (−11.8 to 3.19)	0.24
	Epi cBV [cm^3]		2.78 (1.611)		3.15 (1.71)		3.18 (1.63)	**13.2 (4.04 to 22.5)**	**0.01**	**14.5 (5.84 to 23.1)**	**0.00**
	Epi cBMC [g]		1.32 (0.802)		1.51 (0.844)		1.52 (0.82)	**13.9 (3.82 to 24.0)**	**0.01**	**14.7 (5.45 to 24.0)**	**0.00**
	Met tBMD [g/cm^3]		0.013 (0.052)		0.011 (0.041)		0.005 (0.037)	−26.6 (−119 to 66.2)	0.55	−63.2 (−162 to 35.7)	0.19
	Met cBV [cm^3]		10.3 (2.95)		10.0 (2.91)		10.4 (2.97)	1.49 (−7.68 to 10.7)	0.73	1.18 (−4.81 to 7.17)	0.68
	Met cBMC [g]		6.93 (2.54)		7.08 (2.52)		7.46 (2.66)	7.86 (−1.77 to 17.5)	0.10	**7.65 (1.31 to 14.0)**	**0.02**
	Met CSI [g^2/cm^4]		0.36 (0.211)		0.36 (0.215)		0.361 (0.210)	3.20 (−3.60 to 9.99)	0.33	0.16 (−8.40 to 8.72)	0.97
	Met TSI [cm^3]		1.44 (0.549)		1.44 (0.528)		1.50 (0.545)	4.12 (−0.39 to 8.63)	0.07	**4.63 (1.10 to 8.16)**	**0.01**
	Dia cBV [cm^3]		12.7 (2.85)		12.0 (2.93)		12.7 (2.85)	**−4.26 (−5.57 to −2.95)**	**0.00**	**−3.23 (−4.33 to −2.12)**	**0.00**
	Dia cBMC [g]		10.95 (3.33)		10.8 (3.41)		11.3 (3.31)	1.42 (−0.99 to 3.82)	0.23	**3.01 (1.23 to 4.80)**	**0.00**
TIBIA CT	Epi tBMD [g/cm^3]	17	0.031 (0.039)	14	0.033 (0.04)	17	0.029 (0.038)	7.33 (−3.25 to 17.9)	0.16	−4.53 (−12.6 to 3.58)	0.25
	Epi cBV [cm^3]		2.88 (1.21)		2.99 (1.20)		3.08 (1.20)	**7.56 (1.00 to 14.1)**	**0.03**	**7.00 (0.63 to 13.4)**	**0.03**
	Epi cBMC [g]		1.39 (0.643)		1.47 (0.620)		1.53 (0.643)	**10.8 (3.49 to 18.1)**	**0.01**	**10.2 (3.03 to 17.4)**	**0.01**
	Met tBMD [g/cm^3]		−0.002 (0.043)		0.001 (0.044)		−0.005 (0.044)	377 (−149 to 903)	0.15	**−127 (−219 to −33.8)**	**0.01**
	Met cBV [cm^3]		11.63 (3.10)		11.14 (3.03)		11.2 (2.86)	**−3.71 (−6.13 to −1.29)**	**0.01**	**−4.03 (−6.40 to −1.66)**	**0.00**
	Met cBMC [g]		8.23 (2.80)		8.30 (2.85)		8.36 (2.67)	1.87 (−0.68 to 4.42)	0.14	1.62 (−1.57 to 4.80)	0.30
	Met CSI [g^2/cm^4]		0.474 (0.257)		0.483 (0.270)		0.467 (0.257)	1.01 (−2.48 to 4.49)	0.54	−1.41 (−6.23 to 3.41)	0.54
	Met TSI [cm^3]		1.37 (0.443)		1.41 (0.468)		1.41 (0.440)	**3.35 (1.12 to 5.57)**	**0.01**	2.63 (−0.52 to 5.78)	0.10
	Dia cBV [cm^3]		13.9 (2.86)		13.3 (2.93)		13.4 (2.76)	**−3.40 (−4.72 to −2.08)**	**0.00**	**−3.70 (−5.20 to −2.21)**	**0.00**
	Dia cBMC [g]		11.9 (3.24)		11.8 (3.36)		12.0 (3.12)	0.88 (−0.68 to 2.45)	0.24	0.76 (−1.34 to 2.85)	0.46
FEM	*K* [N m/Degree]	17	17.3 (6.40)	14	17.3 (6.90)	17	17.5 (6.60)	2.40 (−1.54 to 6.40)	0.21	1.41 (−2.30 to 5.14)	0.43
	T_{ult} [N m]		50.8 (20.7)		51.2 (24.0)		51.0 (21.8)	1.80 (−4.17 to 7.80)	0.52	0.28 (−5.00 to 5.60)	0.91
Biomarkers	CTX [ng/mL]	17	0.217 (0.201)	15	0.092 (0.098)	17	0.083 (0.087)	**−60.9 (−92.4 to −29.4)**	**0.00**	**−61.8 (−99.8 to −23.7)**	**0.00**
	P1NP [ng/mL]		99.3 (47.7)		41.8 (24.6)		48.1 (57.7)	**−58.6 (−88.0 to −29.2)**	**0.00**	**−51.5 (−93.8 to −9.27)**	**0.02**
	BSAP [ng/mL]		11.4 (3.91)		7.57 (1.99)		9.65 (6.86)	**−33.9 (−53.5 to −14.2)**	**0.00**	−15.5 (−50.6 to 19.5)	0.36

Mean (SD) measurements across individuals are shown on the left. Mean percent difference (±95% confidence intervals) of follow-up visits compared to baseline are shown on the right. Significant differences from baseline are bolded

Epi epiphyseal, *Met* metaphyseal, *Dia* diaphyseal, *t* trabecular, *c* cortical

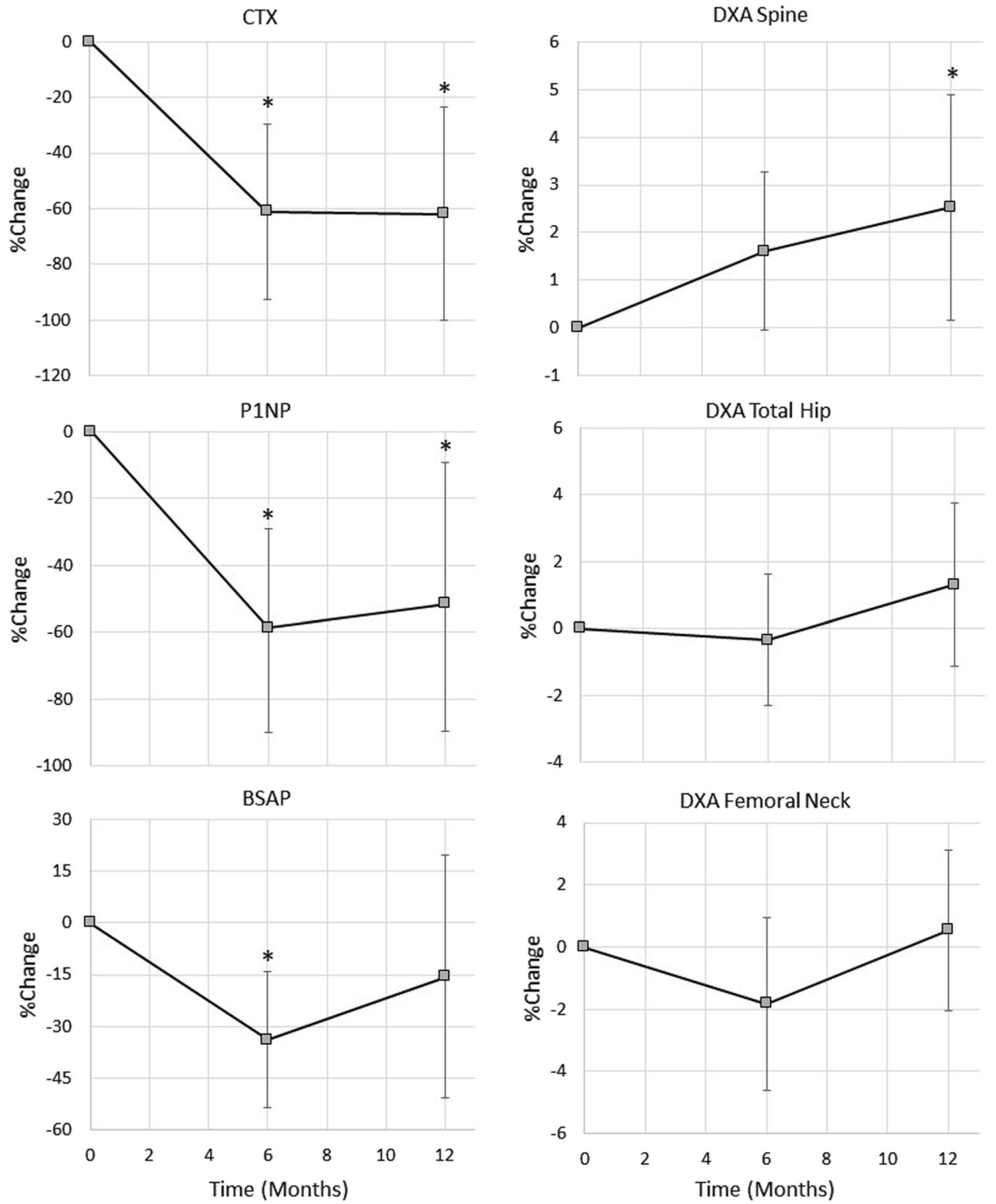

Fig. 1 Mean values (±95% confidence intervals) for serum biomarkers of bone metabolism (left) and select DXA measurements (right) relative to baseline

analog, has also been approved for the treatment of post-menopausal osteoporosis and shown to reduce the risk of vertebral and non-vertebral fractures over 18 months of treatment [34]. Because of the marked skeletal bone loss in many people with long-standing SCI, these anabolic agents would seem to be preferred approaches to rebuilding bone mass and bone strength, thereby reducing fracture risk in this population.

Based on the findings of teriparatide treatment in able-bodied individuals, we initiated and recently completed a randomized controlled trial of teriparatide in 60 people with chronic SCI and low aBMD; this study demonstrated small increases in aBMD at the spine and more limited increases at the hip after 1 and 2 years of treatment [18]. As teriparatide treatment is limited to 2 years, and the increases in bone mass and bone strength were modest, the opportunity

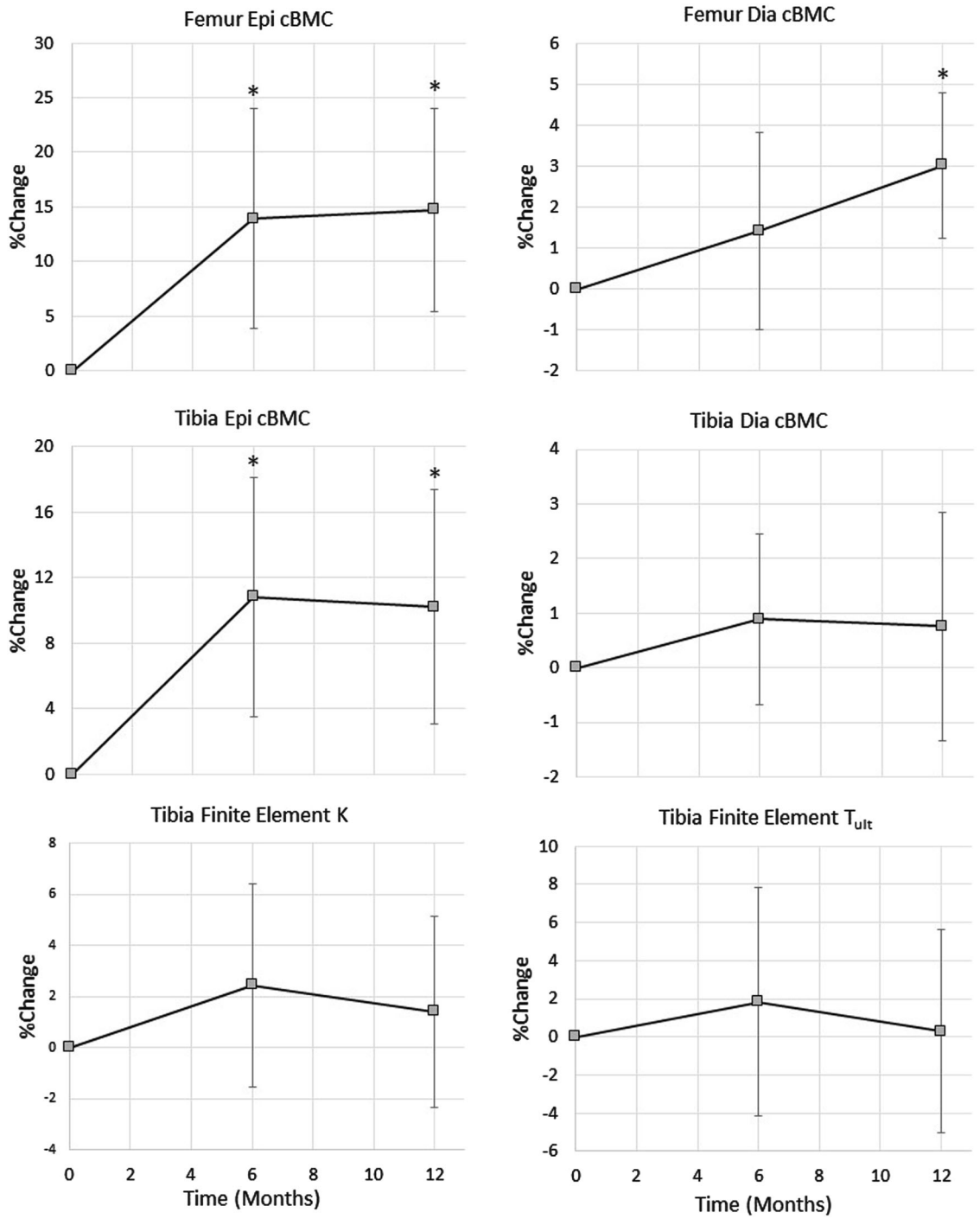

Fig. 2 Mean values (±95% confidence intervals) for select CT measurements at the distal femur (top), select CT measurements at the proximal tibia (middle), and finite element predictions of stiffness (K) and strength (T_{ult}) at the proximal tibia (bottom)

arose to determine if a further year of an oral bisphosphonate, alendronate, would result in maintaining the skeletal benefits of anabolic therapy and perhaps also be associated with further gains in bone mass and/or bone strength. Previous studies with teriparatide in postmenopausal women have demonstrated that discontinuation of teriparatide treatment was followed by loss of aBMD, and that this loss could be prevented by the use of antiresorptive therapy [19, 35]. Results of this study support this notion, as we observed that treatment with alendronate after teriparatide resulted in small gains, or no significant change, at the spine, hip, and many sites of the knee. Reductions were observed at the tibia, a common fracture site in individuals with SCI, but FE modeling suggested no

significant change in bone stiffness or strength at this location. This suggests that these small reductions did not have important effects on the mechanical competence of the bones.

Teriparatide administration results in an increased bone anabolic activity, reflected in an increase in serum bone markers of bone formation such as P1NP and BSAP. However, there is also a marked increase in serum markers of bone catabolic activity (e.g., CTX) with use of teriparatide [36]. After discontinuation of teriparatide, bone formation decreases significantly while bone resorption remains elevated, resulting in subsequent bone loss [19]. The use of bisphosphonates, which work by inhibiting bone resorption, would be expected to prevent this bone loss. This finding has been reported in post-menopausal women after teriparatide treatment [19, 35] and in the current study. Elevated biomarkers of bone turnover, present during teriparatide treatment, were markedly reduced with alendronate therapy in this study. The prevention of bone loss after cessation of teriparatide has also been reported with the use of denosumab [37], an antibody to RANK ligand, which works to inhibit osteoclastogenesis and subsequent bone resorption.

The knee represents the skeletal site most prone to fracture after SCI, and therefore the observed additional improvements in CT-based skeletal parameters at the distal femur following alendronate therapy was encouraging. Although some CT-based measurements at the proximal tibia illustrated significant declines following alendronate therapy (e.g., trabecular BMD and cortical BV at the metaphysis), FE-derived measurements of torsional stiffness and strength were unchanged from the final visit of the parent study, which demonstrated increases in FE-derived stiffness and of 5.0% and 7.4% [18], respectively, suggesting that improvements to skeletal strength were maintained. It is important to note that the finding of a small but beneficial effect of alendronate after cessation of teriparatide therapy for people with SCI and bone loss does not mean that a similar benefit would be seen in a clinical setting without previous anabolic treatment. In chronic SCI, bone formation is depressed, with lower than normal levels of serum markers of anabolic activity [9, 38]. Therefore, additional inhibition of bone formation with an antiresorptive agent, even in the presence of inhibition of bone resorption, would not be expected to provide much, if any, benefit. Indeed, this has been the finding in the majority of studies done to date [39–41]. On the other hand, Zehnder et al. [42] suggested that treatment with alendronate could prevent bone loss without previous anabolic treatment, though it has been suggested that the discrepancy between studies could be due to differences in patient age and lower injury severity [41].

This study has a few noteworthy limitations. This was the second extension offered to individuals in the parent study, and many chose not to continue participating at the end of each stage. As a result, the sample size is quite modest. Furthermore, there were not enough individuals to have a control arm, though this limitation is somewhat mitigated by the fact that it has already been established that cessation of anabolic treatment is associated with a rapid loss of previously gained bone [19–22]. As a result of this small sample size, however, we are unable to draw meaningful conclusions about potential confounding variables such as sex or injury severity.

To summarize, in the setting of completion of a course of bone anabolic therapy, an antiresorptive agent such as alendronate, may provide additional skeletal benefit to people with SCI. With new and more potent anabolic agents available and being actively investigated [34, 43, 44], it may yet be possible to increase and maintain improved bone mass and bone strength in people with long-standing SCI. Though more investigation is required, such treatments could result in a decrease in fracture risk and fracture prevalence in individuals with SCI.

Data archiving

The datasets generated and/or analyzed in this study are available from the corresponding author on reasonable request.

Acknowledgements We would like to thank Stacey M. Lobos for assisting with CT image analysis.

Funding This research was supported by Department of Defense U.S. Army Medical Research and Materiel Command [Grant #SC090010] and the National Institutes of Health's National Center for Advancing Translational Sciences [Grant Numbers UL1TR001422 and UL1TR000150]. The content is solely the responsibility of the authors and does not necessarily represent the official views of these funding agencies.

Author contributions IH: Performed CT image analysis, FE modeling, and statistical analysis of the data. He also helped draft the portions of the initial report. NS: Responsible for data collection, data analysis, and drafting and revising the report. AS: Responsible for data collection, data analysis, and revising the report. FL: Responsible for data collection, data analysis, and revising the report. WBE: Helped with study design. Supervised CT image analysis, FE modeling, and statistical analysis. He was also responsible for interpretation of the data. TS: Designed the study and supervised data collection and statistical analysis tasks. He was also responsible for interpretation of the data. All authors helped to revise the initial report and approved the final submission.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Statement of ethics This study was registered with ClinicalTrials.gov (NCT02195895) and was approved by the Northwestern University Institutional Review Board (IRB) and DOD's Human Research Protection Office (HRPO). Informed consent was obtained prior to the start of any study procedures.

Publisher's note: Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

1. Biering-Sorensen F, Bohr HH, Schaadt OP. Longitudinal study of bone mineral content in the lumbar spine, the forearm and the lower extremities after spinal cord injury. Eur J Clin Invest. 1990;20:330–5.
2. Coupaud S, McLean AN, Purcell M, Fraser MH, Allan DB. Decreases in bone mineral density at cortical and trabecular sites in the tibia and femur during the first year of spinal cord injury. Bone. 2015;74:69–75.
3. Frey-Rindova P, de Bruin ED, Stussi E, Dambacher MA, Dietz V. Bone mineral density in upper and lower extremities during 12 months after spinal cord injury measured by peripheral quantitative computed tomography. Spinal Cord. 2000;38:26–32.
4. Frotzler A, Berger M, Knecht H, Eser P. Bone steady-state is established at reduced bone strength after spinal cord injury: a longitudinal study using peripheral quantitative computed tomography (pQCT). Bone. 2008;43:549–55.
5. Eser P, Schiessl H, Willnecker J. Bone loss and steady state after spinal cord injury: a cross-sectional study using pQCT. J Musculoskelet Neuron Interact. 2004;4:197–8.
6. Battaglino RA, Lazzari AA, Garshick E, Morse LR. Spinal cord injury-induced osteoporosis: pathogenesis and emerging therapies. Curr Osteoporos Rep. 2012;10:278–85.
7. Dionyssiotis Y, Trovas G, Galanos A, Raptou P, Papaioannou N, Papagelopoulos P, et al. Bone loss and mechanical properties of tibia in spinal cord injured men. J Musculoskelet Neuron Interact. 2007;7:62–8.
8. Lazo MG, Shirazi P, Sam M, Giobbie-Hurder A, Blacconiere MJ, Muppidi M. Osteoporosis and risk of fracture in men with spinal cord injury. Spinal Cord. 2001;39:208–14.
9. Lipscomb SD, Zehnder SM. Immersion in the virtual environment: the effect of a musical score on the video gaming experience. J Physiol Anthr Appl Hum Sci. 2004;23:337–43.
10. Gifre L, Vidal J, Carrasco J, Portell E, Puig J, Monegal A, et al. Incidence of skeletal fractures after traumatic spinal cord injury: a 10-year follow-up study. Clin Rehabil. 2014;28:361–9.
11. Nottage WM. A review of long-bone fractures in patients with spinal cord injuries. Clin Orthop Relat Res. 1981;155:65–70.
12. Morse LR, Battaglino RA, Stolzmann KL, Hallett LD, Waddimba A, Gagnon D, et al. Osteoporotic fractures and hospitalization risk in chronic spinal cord injury. Osteoporos Int. 2009;20:385–92.
13. Carbone LD, Chin AS, Burns SP, Svircev JN, Hoenig H, Heggeness M, et al. Morbidity following lower extremity fractures in men with spinal cord injury. Osteoporos Int. 2013;24:2261–7.
14. Frotzler A, Cheikh-Sarraf B, Pourtehrani M, Krebs J, Lippuner K. Long-bone fractures in persons with spinal cord injury. Spinal Cord. 2015;53:701–4.
15. Bethel M, Weaver FM, Bailey L, Miskevics S, Svircev JN, Burns SP, et al. Risk factors for osteoporotic fractures in persons with spinal cord injuries and disorders. Osteoporos Int. 2016;27:3011–21.
16. Neer RM, Arnaud CD, Zanchetta JR, Prince R, Gaich GA, Reginster JY, et al. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. N Engl J Med. 2001;344:1434–41.
17. Kleerekoper M, Greenspan SL, Lewiecki EM, Miller PD, Kendler DL, Maricic M, et al. Assessing the effects of teriparatide treatment on bone mineral density, bone microarchitecture, and bone strength. J Bone Jt Surg Am. 2014;96:e90.
18. Edwards WB, Simonian N, Haider IT, Anschel AS, Chen D, Gordon KE, et al. Effects of teriparatide and vibration on bone mass and bone strength in people with bone loss and spinal cord injury: a randomized, controlled trial. J Bone Min Res. 2018;33:1729–40.
19. Black DM, Bilezikian JP, Ensrud KE, Greenspan SL, Palermo L, Hue T, et al. One year of alendronate after one year of parathyroid hormone (1-84) for osteoporosis. N Engl J Med. 2005;353:555–65.
20. Leder BZ, Neer RM, Wyland JJ, Lee HW, Burnett-Bowie SM, Finkelstein JS. Effects of teriparatide treatment and discontinuation in postmenopausal women and eugonadal men with osteoporosis. J Clin Endocrinol Metab. 2009;94:2915–21.
21. Cohen A, Kamanda-Kosseh M, Recker RR, Lappe JM, Dempster DW, Zhou H, et al. Bone density after teriparatide discontinuation in premenopausal idiopathic osteoporosis. J Clin Endocrinol Metab. 2015;100:4208–14.
22. Prince R, Sipos A, Hossain A, Syversen U, Ish-Shalom S, Marcinowska E, et al. Sustained nonvertebral fragility fracture risk reduction after discontinuation of teriparatide treatment. J Bone Min Res. 2005;20:1507–13.
23. Gordon KE, Wald MJ, Schnitzer TJ. Effect of parathyroid hormone combined with gait training on bone density and bone architecture in people with chronic spinal cord injury. PM R. 2013;5:663–71.
24. Winter DA. Biomechanics and motor control of human movement. 4th ed. Hoboken, N.J.: Wiley; 2009. p. 370. xiv
25. Lang T, LeBlanc A, Evans H, Lu Y, Genant H, Yu A. Cortical and trabecular bone mineral loss from the spine and hip in long-duration spaceflight. J Bone Min Res. 2004;19:1006–12.
26. Edwards WB, Schnitzer TJ, Troy KL. Bone mineral and stiffness loss at the distal femur and proximal tibia in acute spinal cord injury. Osteoporos Int. 2014;25:1005–15.
27. Rho J-Y. An ultrasonic method for measuring the elastic properties of human tibial cortical and cancellous bone. Ultrasonics. 1996;34:777–83.
28. Hill R. A theory of the yielding and plastic flow of anisotropic metals. Proc R Soc Lond Ser A, Math Phys Sci. 1948;193:281–97.
29. Edwards WB, Schnitzer TJ, Troy KL. Torsional stiffness and strength of the proximal tibia are better predicted by finite element models than DXA or QCT. J Biomech. 2013;46:1655–62.
30. Edwards WB, Simonian N, Troy KL, Schnitzer TJ. Reduction in torsional stiffness and strength at the proximal tibia as a function of time since spinal cord injury. J Bone Min Res. 2015;30:1422–30.
31. Edwards WB, Schnitzer TJ, Troy KL. The mechanical consequence of actual bone loss and simulated bone recovery in acute spinal cord injury. Bone . 2014;60:141–7.
32. Cosman F. Parathyroid hormone treatment for osteoporosis. Curr Opin Endocrinol Diabetes Obes. 2008;15:495–501.
33. Whitfield JF, Morley P, Willick GE. Parathyroid hormone, its fragments and their analogs for the treatment of osteoporosis. Treat Endocrinol. 2002;1:175–90.
34. Miller PD, Hattersley G, Riis BJ, Williams GC, Lau E, Russo LA, et al. Effect of abaloparatide vs placebo on new vertebral fractures in postmenopausal women with osteoporosis: a randomized clinical trial. Jama. 2016;316:722–33.
35. Leder BZ, Tsai JN, Jiang LA, Lee H. Importance of prompt antiresorptive therapy in postmenopausal women discontinuing teriparatide or denosumab: the Denosumab and Teriparatide Follow-up study (DATA-Follow-up). Bone. 2017;98:54–8.
36. Black DM, Greenspan SL, Ensrud KE, Palermo L, McGowan JA, Lang TF, et al. The effects of parathyroid hormone and

alendronate alone or in combination in postmenopausal osteoporosis. N Engl J Med. 2003;349:1207–15.
37. Leder BZ, Tsai JN, Uihlein AV, Wallace PM, Lee H, Neer RM, et al. Denosumab and teriparatide transitions in postmenopausal osteoporosis (the DATA-Switch study): extension of a randomised controlled trial. Lancet. 2015;386:1147–55.
38. Reiter AL, Volk A, Vollmar J, Fromm B, Gerner HJ. Changes of basic bone turnover parameters in short-term and long-term patients with spinal cord injury. Eur Spine J. 2007;16:771–6.
39. Vukusich A, Alvear F, Villanueva P, Gonzalez C, Francisco O, Alvarado N, et al. Epidemiology of severe acute renal failure in Metropolitan Santiago. Rev Med Chil. 2004;132:1355–61.
40. Moran de Brito CM, Battistella LR, Saito ET, Sakamoto H. Effect of alendronate on bone mineral density in spinal cord injury patients: a pilot study. Spinal Cord. 2005;43:341–8.
41. Soleyman-Jahi S, Yousefian A, Maheronnaghsh R, Shokraneh F, Zadegan SA, Soltani A, et al. Evidence-based prevention and treatment of osteoporosis after spinal cord injury: a systematic review. Eur Spine J. 2018;27:1798–814.
42. Zehnder Y, Risi S, Michel D, Knecht H, Perrelet R, Kraenzlin M, et al. Prevention of bone loss in paraplegics over 2 years with alendronate. J Bone Min Res. 2004;19:1067–74.
43. Genant HK, Boonen S, Bolognese MA, Mautalen C, Brown JP, Recknor C, et al. Romosozumab administration is associated with significant improvements in lumbar spine and hip volumetric bone mineral density and content compared with teriparatide. Ann Rheum Dis. 2014;73:172.
44. Bandeira L, Lewiecki EM, Bilezikian JP. Romosozumab for the treatment of osteoporosis. Expert Opin Biol Ther. 2017; 17:255–63.

Increasing Bone Mass and Bone Strength in Individuals with Chronic Spinal Cord Injury: Maximizing Response to Therapy

Proposal Log Number BA150039; Award # W81XWH-16-1-0763; HRPO Log A-19839

PI: Dr. Thomas J. Schnitzer **Org:** Northwestern University Feinberg School of Medicine **Award Amount: $489,901**

Study/Product Aims

- Determine effect of treatment with alendronate on bone mass after teriparatide in people with SCI and bone loss.
- Determine effect of treatment with alendronate on bone strength after teriparatide in people with SCI and bone loss.
- Quantify changes in torsional and compressive strength at the distal femur and proximal tibia and correlate with fracture prevalence and incidence.

Approach

This study has two parts: 1) An open-label extension study with alendronate in individuals who had received teriparatide for low bone mass, with DXA BMD, CT BMD and bone markers as outcomes and 2) Analysis of data from that study including finite element modeling to quantify changes in bone mass and bone strength and then correlate these with fracture prevalence in SCI.

IRB approval received at all sites. Enrollment completed. Seventeen subjects have completed the study. Data collected and analyzed. Bone strength modeling and analyses completed.

Timeline and Cost

Activities CY	16	17	18	19
Study Start-Up Activities				
Data Collection and Entry				
Data Analysis				
FEA modeling and analysis				
Estimated Budget ($K)	**$96K**	**$315K**	**$78K**	**$0K**

completed | original projected | current projection

Goals/Milestones

CY16 Goals – Begin study start-up
- Obtain regulatory approval at all sites

CY17 Goals – Complete all data collection.
- Initiate and undertake data analysis for alendronate study
- Obtain CT BMD data parameters, serum bone marker values

CY18 Goal – Completion of all elements of clinical study.
- Complete data analysis and submit publication for alendronate study
- Continue modeling and analysis for bone strength correlations

CY19 Goal
- Complete modeling and analysis for bone strength correlations
- Final study report

Comments/Challenges/Issues/Concerns
- All Goals met; manuscriopt of clinical data currently published; FE modeling accepted as Podium Presentation at ISB/ASB meeting

Budget Expenditure to Date:
Projected Expenditure: $489,901
Actual Expenditure: $489,901

Updated: 24July 2019