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Clinical Trial

Monthly treatment with romosozumab for 1 year increases bone mineral at the hip, but not the knee, in women with chronic spinal cord injury

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Abstract

Bone loss below the level of neurological lesion is a well-known complication of spinal cord injury (SCI). To date, most research has focused on pharmaceutical intervention using antiresorptives to prevent bone loss during the acute phase of SCI; however, limited research has investigated treatments for established osteoporosis during chronic SCI. Romosozumab, a monoclonal antibody with both antiresorptive and anabolic effects, has demonstrated significant increases in BMD for women with established PMO. Therefore, the purpose of this study was to examine the efficacy of monthly treatment with romosozumab to improve DXA-derived areal BMD at the hip, and CT-derived BMC and strength at the hip and knee in women with chronic SCI and an inability to ambulate. Twelve female participants with chronic SCI were recruited to receive 1 yr of monthly subcutaneous injections of romosozumab (210 mg). DXA and CT scans were taken at baseline, and months 3, 6, and 12 to quantify bone mineral, and finite element (FE) analysis was used to predict bone strength. Longitudinal mixed effects models were employed to determine the impact of treatment on bone properties. After 12 mo of treatment, areal BMD at the lumbar spine and total hip were significantly increased with median changes of 10.2% (IQR: 8.3–15.2%, $p<.001$) and 4.2% (IQR: 3.4–7.7%, $p = .009$), respectively. Improvements at the hip were primarily due to increases in trabecular, not cortical, bone and effects were sufficient to significantly increase FE-predicted strength by 20.3% (IQR: 9.5–37.0%, $p = .004$). Treatment with romosozumab did not lead to any significant improvement in bone mineral at the distal femur or proximal tibia. These findings provide promising results for romosozumab treatment to improve bone mineral and reduce fracture risk at the hip, but not the knee, in women with chronic SCI.

Keywords: romosozumab, chronic spinal cord injury, bone mineral, bone strength, finite element analysis

Lay Summary

Spinal cord injury (SCI) is associated with profound bone loss and an increased risk of fracture, particularly at the knee. Previous treatment options to increase BMD in individuals with SCI and osteoporosis have been ineffective. Romosozumab is a novel pharmaceutical treatment for PMO. The purpose of this research was to investigate the effects of monthly treatment with romosozumab on BMD and strength in 12 women with chronic SCI. After 1 yr of treatment, BMD and strength showed marked improvement at the hip, but not the knee, which is the primary anatomical location of interest. Therefore, while romosozumab treatment in chronic SCI shows promise for reducing fracture risk at the hip, fracture risk at the knee is unlikely to be affected.

Introduction

Bone loss is a well-known secondary complication following spinal cord injury (SCI). The loss of bone mineral occurs primarily below the level of neurological lesion due to mechanical disuse and can occur throughout the body due to additional neurogenic and hormonal factors.[1,2] Existing literature demonstrates site-specific, rapid bone loss in the acute phase of SCI (≤6 mo). Within the first 2 yr following injury, the greatest loss in BMC, of ∼50%-60%, is observed at skeletal regions of the knee. Considerable BMC loss is also observed at the proximal femur of the hip, with ∼30%-40% lost at the femoral neck (FN).[3] Though the health impact of bone loss after SCI is not immediately evident, fractures are associated with high morbidity and in some cases mortality.[4] Corresponding with site-specific bone loss, the majority of fractures after SCI occur at the knee and, secondarily, at the hip.[5,6] These post-SCI complications highlight the importance of preserving bone and reducing fractures in this population.

There is no standard of care for the treatment of bone loss after SCI. Active therapies, including functional electrical stimulation, may attenuate bone loss in people with acute (<1 yr) SCI[7] and in some instances improve bone mass in people with chronic SCI,[8] depending on the duration, sessions/week, and stimulus intensity.[9] Of course, the bone response to functional electrical stimulation is limited to bone that spans the stimulated muscle, and the benefits are not sustained after therapy.[9] Research focused on pharmaceutical intervention has mainly examined the efficacy of antiresorptive

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bisphosphonates to prevent bone loss during the acute phase of SCI[10-12]; however, for those diagnosed with secondary osteoporosis during the chronic phase of SCI, anabolic treatments may be beneficial to increase BMD and reduce fracture risk. We previously investigated the efficacy of the anabolic agent teriparatide, a recombinant human parathyroid hormone, within this population.[13] Results demonstrated a significant increase in areal BMD (aBMD) at the spine after 1 yr of teriparatide treatment, but this effect was not clearly demonstrated at the hip or knee,[13] where bone loss and fracture risk are greatest. Therefore, a clear gap in the literature remains the treatment of secondary osteoporosis during chronic SCI.

Romosozumab, a monoclonal antibody sclerostin inhibiter with both antiresorptive and anabolic effects, has demonstrated significant increases in BMD,[14-18] improvement in trabecular bone score[19,20] and reduced fracture risk[14-16,21,22] in women with PMO. Compared with alendronate, both spine and hip aBMD were greater after 12 mo of romosozumab treatment,[15] and, in a separate study, 12 mo of romosozumab treatment resulted in greater increases in both spine and hip bone strength (determined by finite element (FE) modeling) than with teriparatide treatment.[23] The efficacy of romosozumab within the context of post-SCI bone loss has not been established; however, sclerostin plays an integral role in bone remodeling in response to mechanical loading/unloading.[24-27] Indeed, treatment with a sclerostin antibody prevented the bone loss seen with cessation of normal weight-bearing activities in murine models.[28,29]

Based on the involvement of sclerostin in the bone loss pathway due to mechanical disuse, in addition to its successful treatment of PMO, romosozumab has promise to increase bone mineral in chronic SCI. Therefore, the purpose of this study was to examine the efficacy of monthly treatment with romosozumab (210 mg) to improve bone mineral in women with chronic SCI and an inability to ambulate. More specifically, the study objectives included examining the impact of romosozumab treatment on bone mineral at the lumbar spine, the total hip (including its compartmental constituents), and the knee (the distal femur and proximal tibia). We also examined the effect of romosozumab treatment on FE-predicted bone strength at the proximal femur and tibia.

Materials and methods

Study design and participants

A single-center, open-label, prospective cohort pilot study (NCT04708886) beginning on March 1, 2021, was conducted at Northwestern University in Chicago, IL. The clinical trial was carried out in accordance with Good Clinical Practice guidelines and registered at https://clinicaltrials.gov/ct2/show/NCT04708886. The protocol was approved by the Institutional Review Board at Northwestern University (STU00212405) and the Conjoint Health Research Ethics Board at the University of Calgary (REB21-2027). Twelve female participants with chronic SCI were recruited to receive 1 yr of monthly subcutaneous injections of romosozumab (210 mg), followed by 1 yr of oral treatment with weekly alendronate tablets (70 mg). The study is currently ongoing, and herein, this manuscript will refer to the procedures and results related to the first year of the study; treatment with romosozumab.

Study participation was open to adult (18+ yr) females with chronic SCI (6+ mo of injury prior to enrollment) and osteoporosis (T-Score < -2.5 at any skeletal site, or a T-Score < -2.0 with a history of fragility fracture). Participants must have been non-ambulatory at the time of enrollment, as indicated by a Walking Index for Spinal Cord Injury II (WISCI) score of 3 or less. Study participants had to express willingness to complete all study visits. Individuals who were currently pregnant, planning to become pregnant, or currently lactating were excluded from the study and participants of childbearing potential had to be willing and able to use an effective method of contraception or practice abstinence throughout the course of the study and up to 90 d after the last use of the study drug. Participants must have had vitamin D 25-hydroxy levels equal to, or greater than, 20 ng/mL; however, the study protocol allowed for correction and retesting if this criterion was not initially met. Additional inclusion criteria included: normal serum calcium and thyroid stimulating hormone levels and the ability to take oral medication sitting upright for 30 min. Further exclusion criteria included but were not limited to: contraindications for the use of romosozumab or alendronate, heterotopic ossification of the knee, history of bone metastasis, use of any bone-active agents in the last 5 yr, or skeletal malignancies or any other medical condition that would preclude the subject from completing the study (in the opinion of the investigator).

Study visits

As part of the first year of this study, participants underwent 14 visits to the research clinic. The initial screening visit included an explanation of the study. Informed consent was obtained, medical history was recorded, and the Spinal Cord Injury & Lifestyle Information (SCILI) was collected from each participant. Vital signs and physical examination were performed, electrocardiogram, and blood and urine were obtained for screening testing (hematology, chemistry, endocrine parameters, pregnancy, vitamin D levels). A DXA scan was performed, and the WISCI assessment was administered at this visit. Those individuals with low vitamin D levels were given an 8-wk supply of 50 000 IU vitamin D to be taken once a week and returned for a blood draw to establish adequate levels of vitamin D prior to initiation of romosozumab treatment. Each participant had a baseline visit within 8 wk following initial screening. At this visit, inclusion/exclusion criteria were verified, and CT scans of the hip and knee were performed. Participants then received their first dose of romosozumab and were dispensed vitamin D and calcium with instructions for their daily administration. A WISCI assessment was also performed.

Monthly visits following baseline included recording of vital signs, adverse events (AEs), changes to concomitant medications, periodic measurements of serum calcium and vitamin D for safety, and romosozumab treatment administration. At months 3, 6, and 12, WISCI scores were reassessed, and DXA and CT scans were completed (with the exception of CT scans of the hip, which were not included at month 3). Pregnancy tests were completed prior to imaging and dosing at all visits, where applicable.

DXA imaging

DXA measurements performed at screening, and months 3, 6, and 12 included bilateral total hip, bilateral FN, and lumbar spine to quantify aBMD at all locations. Unless precluded

by the presence of an artifact (eg, hardware, previous fracture), the non-dominant side was chosen for the hip analysis. The presence of hardware precluding imaging of the lumbar spine was not exclusionary; however, unless a minimum of 2 vertebrae without artifact were available for interpretation and analysis of aBMD, the lumbar spine sample was removed from the study results. Scans were performed using a QDR 4500A DXA system (Hologic, Inc., Waltham, MA, United States). All scans for a given participant were collected on a single machine and quality control was regularly performed. Day-to-day coefficients of variation of the spine phantom and hip measurements have been previously reported in this research facility at 0.387%[30] and 0.400%,[31], respectively. Standard image acquisition protocols[32] were used to quantify aBMD at the lumbar spine, total hip, and FN. One qualified personnel completed 100% of the DXA scans for this study, and previously reported intra-class correlation coefficients exceeded 0.97 in this research facility.[30]

CT imaging

Computed tomographyscans at baseline, and months 3, 6, and 12 were used to examine volumetric bone mineral at the knee (distal femur and proximal tibia) and hip (FN and trochanteric regions). The CT scans were performed using a Siemens Somatom machine (120kVp, 280 mAs, pixel size 0.352 mm, slice thickness 1 mm). Each CT scan included a phantom placed on the side of, or underneath, the subject's knee or hip to fit within the field of view. The phantom had known calcium hydroxyapatite concentrations of 0, 0.4, and 0.8 g/cm^3 (QRM, Moehrendorf, Germany). The phantom served as an interscan calibration, allowing for the conversion of CT Hounsfield units to bone equivalent density for analysis.

Analysis of bone mineral was conducted with a protocol similar to a previous study in our lab.[33,34] Manual manipulation of baseline images for each participant in Materialise Mimics Software (Leuven, Belgium) was completed to realign each bone along the tibial diaphyseal, femoral diaphyseal, or FN axes. Follow-up images were then registered into their respective aligned baseline images using a previously reported registration procedure.[33,34] Proximal tibial, distal femoral, and proximal femoral regions were then further subdivided into integral, trabecular, and cortical compartments. Compartmental bone measurements were computed separately for the epiphyseal and metaphyseal locations at the knee as well as FN and trochanteric regions at the hip. Within each region and compartment, we recorded bone volume (BV) and volumetric BMC and BMD. A graphical summary of the regions of interest for the proximal femur and proximal tibia have been included in the Supplementary Material Figure S1. The root-mean-square coefficient of variation for intra-operator precision of the CT analysis protocol was estimated to range from 0.3 to 2.7% in acute SCI,[33] but precision errors in the chronic SCI setting have not yet been established.

FE analysis

CT-based FE modeling was used to estimate bone strength (ie, failure load) at the proximal femur and proximal tibia. The modeling approaches for both bones were previously reported and validated against experimental data[35-37] and used as biomechanical outcome measures in clinical trials evaluating pharmaceutical therapies for bone loss after SCI.[13,38,39] Briefly, voxels comprising the proximal femur and proximal tibia were directly converted to 8-node hexahedral elements with an isotropic edge length of 1.5 mm. Elements were assigned nonlinear and inhomogeneous material properties based on bone apparent density at each element location. Proximal femoral models were positioned in a sideways fall configuration with the greater trochanter being the point of impact.[40] Six centimeters of polymethyl methacrylate (PMMA) was modeled as a conforming mesh around the head of the femur and base of the greater trochanter.[41] A ramped vertical load was applied to the center of the PMMA at the femoral head, while the base of the greater trochanter was vertically constrained. Rotational and axial constraints were placed around the femoral shaft, below the lesser trochanter. Proximal femoral strength, or failure load, was calculated as the force at 4% deformation of the femoral head with respect to the greater trochanter.[41] The proximal tibia models were longitudinally aligned and loaded in pure torsion, as spiral fractures are frequently observed around the knee in the SCI population.[42,43] A torsional displacement was applied to surface nodes of the proximal-most 2 cm of bone and surface nodes below the proximal-most 13 cm of bone were fixed in translation. The reaction torque was monitored and failure load was calculated when a specific percentage of surface elements had failed according to a maximum principal strain criterion.[36] All FE models were solved using ABAQUS 2020 (ABAQUS Inc., Providence, RI).

Statistical analyses

DXA-derived aBMD at the lumbar spine, total hip, and FN were treated as the primary outcome variables for this study and had an alpha level of 0.017 to adjust for multiple comparisons. CT-derived measures of integral, trabecular, and cortical BMC and BV at the FN of the hip, and distal femur and proximal tibia of the knee were treated as secondary outcomes. FE-predicted strength at the proximal femur and tibia were tertiary study outcomes. Secondary and tertiary outcomes were not adjusted for multiple comparisons and had an alpha level of 0.05 to reduce the likelihood of type II error in the CT and FE analyses; however, this leads to elevated potential for type I error, thus findings for secondary and tertiary outcomes should be interpreted with caution. Descriptive statistics of study variables were calculated as counts (percentages) for categorical variables, and means (±SDs) or and medians (IQR) for continuous variables. A series of longitudinal mixed effects models were used to evaluate the effect of romosozumab over 1 yr of treatment. This statistical analysis technique was used to allow each participant to be analyzed with a unique treatment effect on outcome variables. Correlation analyses were used to determine relationships between DXA-derived aBMD and CT-derived volumetric BMD (vBMD) at the total hip, as well as CT-derived proximal femur and tibia vBMD and FE-predicted strength at respective locations. All statistical analyses were completed using STATA 17.0 software.

Results

Participants

Complete demographic information for the sample of 12 female participants with chronic SCI recruited for this trial is provided in Table 1. Most participants ($n = 11$) had a complete

Table 1. Baseline demographic information.

Parameter ($n = 12$)	
Age (years), mean (±SD)	45.4 (±9.1)
Menopausal status, *n* (%)	
Premenopausal	7 (58%)
Postmenopausal	5 (42%)
BMI (kg/m^2), mean (±SD)	23.5 (±4.4)
Race, *n* (%)	
Asian	1 (8%)
Black/African American	1 (8%)
White	10 (83%)
WISCI level, mean (±SD)	0 (0.0)
Time since SCI (years), mean (±SD)	15.1 (±11.2)
ASIA Impairment Scale, *n* (%)	
A	8 (67%)
B	3 (25%)
C	1 (8%)
D	0 (0%)
Injury severity, *n* (%)	
Motor Complete	11 (92%)
Motor Incomplete	1 (8%)
Level, *n* (%)	
Cervical	3 (25%)
Thoracic	9 (75%)
Lumbar	0 (0%)

SCI at the thoracic ($n = 9$) or cervical level ($n = 3$), with an average time since injury of 15.1 (±11.2) yr at study baseline. Participants were also mostly Caucasian and the average age of participants was 45.4 (±9.1) yr. All but 1 participant received 12 subcutaneous injections of romosozumab, while 1 participant received 11 injections. As indicated in the Online Supplementary Material Figure S2, 11 participants continued into the second treatment phase of this trial, which is currently ongoing.

DXA assessment

A significant effect of romosozumab treatment over time was observed for aBMD at the lumbar spine ($p < .001$), total hip ($p = .009$), and FN ($p < .001$). Medians (IQRs) demonstrated a general increase in aBMD over the year (Table 2), with relative gains in aBMD of 10.2% (IQR: 8.3%–15.2%, $p < .001$) at the lumbar spine, 4.2% (IQR: 3.4%–7.7%, $p = .009$) at the total hip, and 7.5% (IQR: 0.7%–10.9%, $p < .001$) at the FN, as seen in Figure 1A and B. As seen in Figure 1B, 1 participant demonstrated a notably large change in total hip aBMD; therefore, as a precaution, the statistical analysis of this outcome was repeated after removing the participant, and the treatment effect over 1 yr remained statistically significant ($p < .001$). At baseline, 10 participants had hip T-Scores in the osteoporotic range (T-Score = −2.5 or lower) and 2 participants were in the osteopenic range (T-Score = −1.0 to −2.4), and all participants remained the same classification after 1 yr of treatment, meaning there was a significant improvement with treatment, but not enough to change the diagnostic classification of osteoporosis.

Hip CT assessment

A significant effect of romosozumab treatment over time was observed for integral ($p = .022$) and trabecular ($p = .002$) BMC at the FN and trabecular BMC ($p = .046$) at the trochanteric region, but not cortical BMC ($p > .169$) at either anatomical location (Table 3). Despite an increase in BMC, BV did not significantly change at the FN or trochanteric region of the hip. Median percentage changes after 1 yr demonstrated an increase in integral and trabecular BMC at the FN of 3.7% and 10.9%, respectively. While a statistically significant improvement was seen in trabecular BMC at the trochanteric region, median percent change at 1 yr was −1.5%, demonstrating that individual effects were mixed in this sample. Total hip aBMD, as measured by DXA, significantly correlated ($p < .001$) with total integral vBMD of the hip, as measured by the CT (found in Supplementary Table S1), with an $R^2 = 0.74$, suggesting coherence in results between the 2 imaging modalities.

Knee CT assessment

A significant effect of romosozumab treatment over time was not observed for epiphyseal integral ($p = .273$) and trabecular ($p = .143$) BMC or metaphyseal integral BMC ($p = .092$) at the distal femur (Table 4); however, cortical BMC at the distal femur significantly decreased over the course of treatment ($p = .017$), with a median loss of 15.6% after 12 mo. At the proximal tibia, epiphyseal integral ($p = .214$) and trabecular ($p = .071$) BMC did not demonstrate significant treatment effects over time, while epiphyseal cortical BMC ($p = .018$) and metaphyseal integral BMC ($p = .025$) both demonstrated significant decreases over the course of treatment, with median losses of 19.0% and 3.0% at month 12, respectively. Notably, some trabecular BMC values were negative, which has previously been reported in chronic SCI[44] and is indicative of voxels comprised primarily of marrow fat rather than bone.

FE *analyses*

A significant effect of romosozumab treatment over time was observed for FE-predicted strength at the proximal femur ($p = .004$; Table 3), with a median increase of ∼20.3% after 1 yr (Figure 1C). Total integral BMC at the hip, as calculated by CT, was significantly associated with proximal femoral strength with a low observed correlation ($R^2 = 0.177$, $p = .011$). No effect of romosozumab treatment over time was observed for FE-predicted torsional strength at the proximal tibia ($p = .845$; Table 4). Total integral BMC at the proximal tibia, as calculated by CT, was significantly associated with tibia torsional strength with a high observed correlation ($R^2 = 0.884$, $p < .001$). A representative model illustrating the predicted strain distribution at the proximal femur for a fixed arbitrary load can be seen in Figure 2. Post hoc analyses were completed to investigate any joint effects of injury duration or menopausal status with treatment throughout 1 yr on FE-predicted hip strength. There was a significant interaction ($p = .032$) between injury duration at baseline and treatment effect at the 6-mo timepoint. There was no significant effect of menopausal status ($p = 0.316$) on FE-predicted hip strength.

Safety outcomes

No unanticipated problems involving risk to participants or others occurred in this study. All 12 participants reported at least 1 AE, with 79 total reported AEs, including 33 that were possibly or definitely related to study procedures or drug. No AEs reported during the 12 mo of treatment with romosozumab were classified as serious. The most com-

Table 2. Median and IQR at baseline, months 6 and 12 (median percent change from baseline and IQR) for DXA results at the lumbar spine and hip (alpha value of 0.017).

	Timepoint	Median	IQR	Median % change	IQR % change	*p*-value
Lumbar Spine aBMD (g/cm^2)	Baseline	1.02	0.94 – 1.21			**<.001**
	Month-6	1.11	1.05 – 1.28	+7.59%	4.35 – 11.68	
	Month-12	1.17	1.06 – 1.31	+10.16%	8.26 – 15.22	
Total Hip aBMD (g/cm^2)	Baseline	0.51	0.48 – 0.59			**=.009**
	Month-6	0.54	0.50 – 0.62	+2.56%	0.74 – 5.47	
	Month-12	0.54	0.51 – 0.62	+4.22%	3.43 – 7.66	
FN aBMD (g/cm^2)	Baseline	0.54	0.43 – 0.58			**<.001**
	Month-6	0.53	0.43 – 0.63	+1.44%	−2.78 – 11.61	
	Month-12	0.58	0.48 – 0.62	+7.52%	0.72 – 10.86	

Significant *p*-values are highlighted in bold.

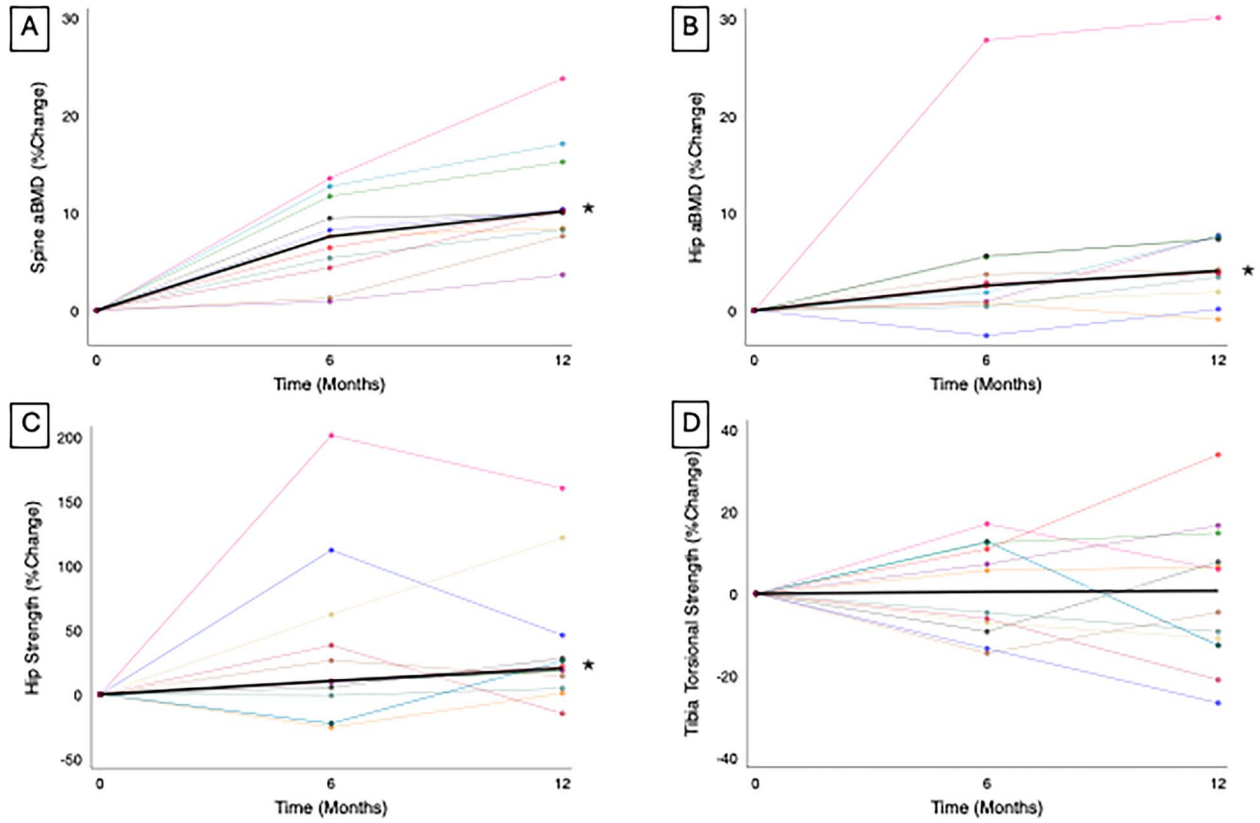

Figure 1. Individual percent change (thin lines) in aBMD at the lumbar spine (A) and total hip (B), and FE-predicted strength at the proximal femur (C) and proximal tibia (D), over 12 mo of romosozumab treatment, with median percent change (thick lines). Each participant is represented by the same color across the 4 graphs. An asterisk (∗) indicates a significant treatment effect. Statistical models employed absolute values, not percent change.

mon AEs that may have been related to study procedure or drug included mild-to-moderate injection site reaction ($n = 14$), myalgia ($n = 4$), bone pain ($n = 3$), headache ($n = 3$), and arthralgia ($n = 3$). All but 1 case of arthralgia had resolved.

Discussion

Rapid and profound bone loss is a well-known secondary complication following SCI.[1,2] While the magnitude of bone loss begins to plateau ∼2 yr after injury,[3] clinical osteoporosis and elevated fracture risk remain a major concern in the chronic phase of SCI. Increasing BMD and decreasing fracture risk, especially at the hip and knee, is a clinical priority for these patients; however, limited research has been conducted for treatment options in chronic SCI. Within the very limited existing literature, the anabolic agent teriparatide was not fully effective,[13] therefore, further investigation of bone building agents to improve bone mineral in this population is necessary. Thus, the purpose of this study was to investigate 1 yr of treatment with the monoclonal antibody, romosozumab, on bone mineral and strength in women with chronic SCI. In general, 1 yr of romosozumab treatment led to increases in bone mineral at the hip and spine, but not the knee.

As indicated in Figure 1A and B, romosozumab treatment significantly increased aBMD at both the lumbar spine and hip after 1 yr with 10 and 4% median gains, respectively. These results are consistent with findings related to romosozumab treatment of PMO, which have also demonstrated significant improvement after 1 yr, with a slightly greater impact at the lumbar spine than hip.[14,15,16,17] A notable difference between our sample and the PMO population is that our

Table 3. Median and IQR at baseline, months 6 and 12 (median and IQR percent change from baseline) for CT and FE analysis at the hip (alpha value of .05).

	Timepoint	Median	IQR	Median % change	IQR % change	*p*-value
FNiBV (cm^3)	Baseline	19.74	19.21 – 23.06			=.119
	Month-6	20.18	19.11 – 23.40	+1.00%	−1.95 – 3.55	
	Month-12	20.83	19.16 – 25.05	+0.00%	−0.70 – 1.73	
FNiBMC (g)	Baseline	5.00	3.58 – 5.96			**=.022**
	Month-6	5.01	3.11 – 6.38	+0.96%	−8.11 – 5.19	
	Month-12	5.15	3.69 – 6.86	+3.70%	−1.87 – 14.98	
FNtBV (cm^3)	Baseline	6.41	5.56 – 7.62			=.155
	Month-6	6.43	5.53 – 8.10	+1.34%	−0.71 – 3.02	
	Month-12	6.75	5.67 – 7.98	+1.39%	−0.05 – 3.38	
FNtBMC (g)	Baseline	0.13	−0.03 – 0.41			**=.002**
	Month-6	0.13	−0.02 – 0.54	−23.28%	−62.49 – 54.04	
	Month-12	0.20	0.02 – 0.47	+10.94%	−98.35 – 44.87	
FNcBV (cm^3)	Baseline	5.30	3.83 – 6.41			=.070
	Month-6	5.38	3.16 – 6.60	+1.06%	−9.25 – 4.65	
	Month-12	5.76	4.07 – 7.08	+3.56%	−7.77 – 16.77	
FNcBMC (g)	Baseline	3.58	2.34 – 4.15			=.169
	Month-6	3.53	1.94 – 4.15	−1.91%	−11.73 – 4.41	
	Month-12	3.66	2.40 – 4.47	+1.59%	−13.09 – 16.74	
TRiBV (cm^3)	Baseline	62.22	56.64 – 76.28			=.126
	Month-6	62.21	54.87 – 76.18	−0.30%	−1.63 – 0.32	
	Month-12	62.01	51.12 – 75.94	+0.03%	−1.34 – 1.39	
TRiBMC (g)	Baseline	10.60	8.10 – 12.95			=.737
	Month-6	11.68	8.34 – 13.46	+0.40%	−6.42 – 7.19	
	Month-12	10.65	8.84 – 12.74	+5.42%	−8.18 – 9.62	
TRtBV (cm^3)	Baseline	24.48	21.10 – 30.93			=.239
	Month-6	24.50	20.10 – 30.71	−0.11%	−0.94 – 0.78	
	Month-12	24.76	19.99 – 30.80	+0.63%	−1.22 – 1.95	
TRtBMC (g)	Baseline	0.09	−0.73 – 0.34			**=.046**
	Month-6	0.14	−0.67 – 1.02	+12.42%	−28.46 – 62.80	
	Month-12	0.21	−0.36 – 0.68	−1.49%	−42.07 – 47.11	
TRcBV (cm^3)	Baseline	10.44	8.88 – 13.46			=.891
	Month-6	11.52	9.00 – 13.67	−0.53%	−7.36 – 6.26	
	Month-12	11.02	8.94 – 12.93	+1.42%	−13.16 – 9.70	
TRcBMC (g)	Baseline	6.78	5.67 – 9.18			=.753
	Month-6	7.34	5.87 – 8.96	−5.47%	−12.98 – 4.61	
	Month-12	7.06	5.45 – 8.51	−2.30%	−18.61 – 6.88	
Femoral Strength (N)	Baseline	1456.45	1048.85 – 1702.25			**=.004**
	Month-6	1743.80	1421.50 – 2173.05	+10.56%	2.28 – 50.02	
	Month-12	1991.25	1339.70 – 2488.75	+20.29%	9.48 – 37.00	

Abbreviations: BMC, bone mineral content; BV, bone volume; c, cortical region; FN, femoral neck; i, integral region; t, trabecular region; TR, trochanteric.

participants had non-osteoporotic T-Scores at the spine, thus our results demonstrate that romosozumab is still effective at increasing aBMD in the non-osteoporotic spine. Because we had 2 imaging modalities investigating bone mineral at the hip, we ran a correlation analysis which demonstrated a significant relationship ($R^2 = 0.74$, $p < .001$) between total hip aBMD, as measured by DXA, and total integral vBMD at the hip, as measured by CT. This indicates congruency between results provided by the 2 imaging modalities, confirming the treatment is effectively increasing bone mineral at the hip. The CT images allowed us to proceed with a more detailed analysis of the compartmental constituents of the proximal femur not seen through the DXA.

CT results indicated significant increases in trabecular bone at both the FN and trochanteric regions of the hip, but no improvement in cortical bone at either location. These results suggest that romosozumab tends to affect trabecular bone more than cortical bone, possibly due to increased surface area for drug activity. Effects may also be present in trabecular bone for which bone loss following injury has plateaued, compared with cortical bone, which may experience continued losses into the chronic SCI phase, thereby, making it more difficult to establish improvements with treatment. A previous study exploring changes in bone mass for individuals with chronic SCI demonstrated no significant change in tibial trabecular vBMD over a 2-yr study duration, but did demonstrate a significant unadjusted reduction in tibial cortical vBMD.[45]

Importantly, CT-based FE modeling of the proximal femur demonstrated a significant increase in bone strength over 1 yr of treatment with romosozumab, indicating that the increase in trabecular, but not cortical bone, at the hip, was sufficient to improve bone strength by a median of 20%. In other words, improvement in some, but not all, compartmental constituents of bone at the hip was sufficient to indicate promise for reduced fracture risk with romosozumab treatment in this sample. It is interesting to also note that relative improvements in femoral strength were some 5 times greater than those observed for aBMD (ie, median changes of 20 vs. 4%), indicating that bone mineral accrual occurred in mechanically relevant locations.

Contrary to the hip, CT results at the distal femur and proximal tibia of the knee demonstrated no improvement in any compartmental constituents of bone with romosozumab

Table 4. Median and IQR at baseline, months 6 and 12 (median and IQR percent change from baseline) for CT and FE analysis results at the knee (alpha value of .05).

	Timepoint	Median	IQR	Median % change	IQR % change	*p*-value
	Distal Femur CT					
Epi iBMC (g)	Baseline	9.00	5.51 – 12.08			=.273
	Month-6	8.47	5.26 – 11.39	−5.01%	−14.82 – 4.23	
	Month-12	8.84	5.09 – 11.65	−6.64%	−9.98 – 1.08	
Epi tBMC (g)	Baseline	1.10	−0.26 – 2.19			=.143
	Month-6	0.85	−0.25 – 2.00	−22.60%	−41.18 – 7.07	
	Month-12	1.27	−0.39 – 1.87	−12.21%	−20.74 – 28.31	
Epi cBMC (g)	Baseline	2.04	0.82 – 2.87			**=.017**
	Month-6	1.31	0.63 – 2.08	−23.34%	−29.69 – −19.20	
	Month-12	1.23	0.90 – 2.19	−15.64%	−24.43 – −4.04	
Met iBMC (g)	Baseline	7.93	5.46 – 10.00			=.092
	Month-6	7.59	5.76 – 9.35	−5.62%	−8.73 – 1.17	
	Month-12	7.65	5.07 – 9.54	−6.35%	−11.52 – −2.33	
	Proximal Tibia CT					
Epi iBMC (g)	Baseline	5.87	3.62 – 8.36			=.214
	Month-6	5.92	3.43 – 7.62	−2.30%	−14.25 – 4.07	
	Month-12	3.66	3.21 – 8.19	−6.33%	−11.50 – 1.75	
Epi tBMC (g)	Baseline	0.04	−0.91 – 0.38			=.071
	Month-6	−0.12	−0.95 – 0.47	−13.47%	−29.56 – 22.80	
	Month-12	0.13	−1.1 – 0.43	−0.00%	−34.16 – 58.56	
Epi cBMC (g)	Baseline	1.53	0.76 – 2.62			**=.018**
	Month-6	1.07	0.63 – 2.00	−26.26%	−29.44 – −15.60	
	Month-12	1.30	0.87 – 1.97	−19.04%	−22.56 – 10.25	
Met iBMC (g)	Baseline	7.99	5.55 – 10.12			**=.025**
	Month-6	7.81	5.58 – 9.27	−1.95%	−4.78 – 0.53	
	Month-12	7.97	5.38 – 9.28	−2.97%	−8.11 – −0.60	
Torsional Strength (N)	Baseline	35.89	28.36 – 52.00			=.845
	Month-6	38.88	29.25 – 51.36	+0.48%	−8.19 – 11.63	
	Month-12	40.92	27.92 – 50.52	+0.69%	−11.80 – 11.22	

Abbreviations: BMC, bone mineral content; c, cortical region; Epi, epiphyseal; i, integral region; Met, metaphyseal; t, trabecular region.

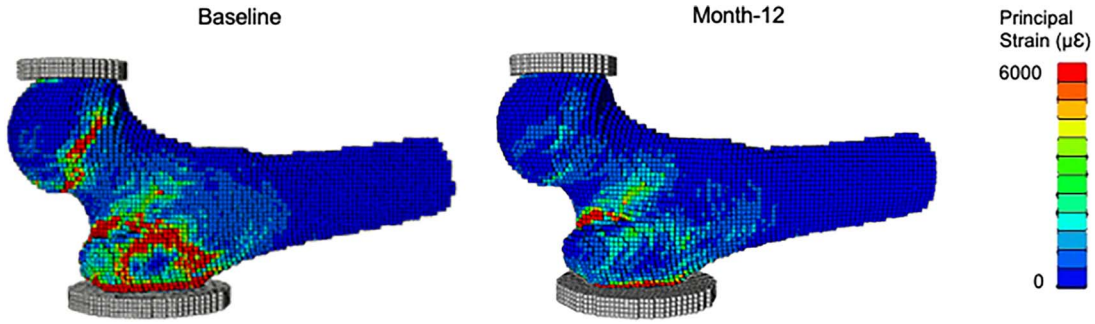

Figure 2. A representative example of the FE-predicted strain distributions at baseline and after 1 yr of treatment. Images are shown at a fixed arbitrary load, which is lower than the failure load of these bones. Strains were largest at the FN and greater trochanteric region at baseline with a notable decrease in strain at these regions after treatment.

treatment, and results trended toward continued loss of cortical and integral bone mineral. Furthermore, FE modeling of the proximal tibia confirmed there was no significant impact of treatment on torsional strength over 1 yr. Notably, in the SCI population, the majority of fractures occur at skeletal regions of the knee[5,6]; therefore, the lack of improvement in bone mineral and strength at the knee with romosozumab treatment is an unfortunate finding, as a major clinical concern is not being addressed. These results are difficult to contextualize within existing romosozumab literature as PMO studies frequently provide indication of changes in bone mineral at the lumbar spine and hip, but not the knee. A plausible contributor to the discrepancy between treatment response at the lumbar spine/hip and the knee are sclerostin levels, which may be impacting the mechanism of action of romosozumab. A publication by Morse et al. (2012) indicated that in people with chronic SCI, sclerostin levels were significantly associated with aBMD at the distal femur and proximal tibia of the knee, but not the radius of the arm. For the majority of study participants with chronic SCI, the knee experienced mechanical unloading, but the radius did not. Therefore, the authors indicated that local reductions in sclerostin production may occur with sublesional bone loss.[46] Based on this theory, it is possible that in our study, lower sclerostin levels were present at the knee (with complete mechanical unloading) than the lumbar spine and hip (with some mechanical loading), and therefore, the sclerostin inhibitor romosozumab was less effective at the knee.

In addition to the aforementioned work by Morse et al. (2012), Battaglino et al. (2012) also reported sclerostin levels following SCI, indicating that circulating sclerostin is greatest within the first 5 yr following SCI.[47] If sclerostin levels are

elevated in the more acute SCI phase, and are reduced in the chronic phase, it may be suggested that romosozumab, a sclerostin inhibitor, may be a more beneficial treatment in the acute phase during this period of heightened sclerostin. While our study participants were all considered to be in the chronic SCI phase, they had a mean injury duration of 15.1 (±11.2) yr, with participants ranging from 2.3 to 34.0 yr of injury at baseline. Therefore, when contextualizing our results within the sclerostin and SCI literature, a post hoc analysis of the impact of injury duration on treatment effect was conducted for the composite measure of FE-predicted hip strength. This indicated a significant interaction (p = .032) between injury duration at baseline and treatment effect at the 6-mo timepoint. Interestingly, the 2 participants that had notably larger improvements in hip strength at the 6-mo timepoint (see Figure 1C) were on the lowest end of the injury duration range, at just 2.3 and 2.9 yr since injury at study enrollment. One of these participants was also a high responder who experienced the greatest percent increase in aBMD (∼30%, see Figure 1B), and total integral vBMD, throughout the study duration. These 2 case results are consistent with literature suggesting that romosozumab may have a greater impact in the acute and early chronic phases when sclerostin levels are elevated. Notably, this high responding participant had given birth 8 wk prior to baseline, which may have contributed to these results. Existing literature has demonstrated a trend toward decreased aBMD at the hip during pregnancy,[48] which may be recovered in the postpartum period. One case report demonstrated an increase in spine and hip aBMD with romosozumab treatment after pregnancy in a non-SCI individual.[49] Despite the potential contributions due to recent pregnancy, it remains possible that individuals from our study in the early years of SCI were greater responders to romosozumab treatment and further investigation is required for confirmation.

While these results suggest romosozumab is a promising treatment option to improve bone mineral and strength at the hip, but not the knee, during chronic SCI, there are a few limitations within our study. This clinical trial had a small sample size of 12 women with chronic SCI, and therefore, while our results provide a preliminary indication of treatment effect, this investigation should be repeated with a larger sample size for more robust results. Furthermore, we were unable to include measures of bone turnover markers, which can provide additional information regarding response to treatment. This study was limited to a sample of women with chronic SCI and cannot be generalized to men with chronic SCI, or individuals with acute SCI. Finally, this was not a randomized controlled trial as all participants received treatment and a comparator analysis to a control group could not be performed. A previous 5-yr longitudinal bone evaluation in individuals with chronic SCI and no treatment indicated a nonsignificant trend toward improvement in spine and hip aBMD, but a trend toward loss of distal femur and proximal tibia aBMD.[50] Thus, in chronic SCI, bone mineral at the lumbar spine and hip is better conserved than at the knee, even without treatment. This phenomenon could be confounding the treatment effect demonstrated in our study, but we suspect that contribution to be low.

Conclusions

One year of romosozumab treatment in women with chronic SCI increased DXA-derived aBMD at the lumbar spine and hip. These results were congruent with CT results at the hip, which indicated increases in trabecular, but not cortical, bone mineral, as well as significant improvements in proximal femoral strength predicted with FE modeling. Romosozumab treatment did not illustrate corresponding increases in bone mineral at the knee, and there was no impact of treatment on FE-predicted torsional strength at the proximal tibia. Therefore, our study provides promising results for romosozumab treatment to improve bone mineral and reduce fracture risk at the hip, but not the knee, in this population.

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Author contributions

Laura Crack (Formal analysis, Investigation, Methodology, Writing—original draft, Writing—review & editing), Narina Simonian (Data curation, Formal analysis, Investigation, Methodology, Project administration, Writing—review & editing), Thomas Schnitzer (Conceptualization, Funding acquisition, Methodology, Resources, Supervision, Writing—review & editing), and William Edwards (Conceptualization, Methodology, Resources, Software, Supervision, Writing—review & editing).

Supplementary material

Supplementary material is available at *JBMR Plus* online.

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Conflicts of interest

L.E.C. and N.S. have no competing interests to declare.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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