BMJ Open

Exoskeletal-assisted walking combined with transcutaneous spinal cord stimulation to improve bone health in persons with spinal cord injury: study protocol for a prospective randomised controlled trial

Christopher M Cirnigliaro ,[1,2] William Kuo,[3] Gail F Forrest,[2,4] Ann M Spungen,[1,5] J Scott Parrott,[6] Christopher P Cardozo,[1,5] Saikat Pal,[7] William A Bauman[5]

To cite: Cirnigliaro CM, Kuo W, Forrest GF, *et al*. Exoskeletal-assisted walking combined with transcutaneous spinal cord stimulation to improve bone health in persons with spinal cord injury: study protocol for a prospective randomised controlled trial. *BMJ Open* 2024;**14**:e086062. doi:10.1136/bmjopen-2024-086062

► Prepublication history for this paper is available online. To view these files, please visit the journal online (https://doi.org/10.1136/bmjopen-2024-086062).

Received 04 March 2024
Accepted 28 August 2024

For numbered affiliations see end of article.

Correspondence to
Dr Christopher M Cirnigliaro; christopher.cirnigliaro@gmail.com

ABSTRACT

Introduction Persons with non-ambulatory spinal cord injury (SCI) undergo immediate unloading of the skeleton and, as a result, have marked loss of bone mineral density below the level of lesion that is directly associated with increased risk of long-bone fractures. There is a paucity of research that has successfully implemented rehabilitation and/or exercise training interventions to mitigate bone loss after acute SCI or reverse bone loss that has already occurred in chronic SCI. This paper describes a research protocol to compare the effect of exoskeletal-assisted walking (EAW) alone versus EAW plus transcutaneous spinal cord stimulation (EAW+tSCS) on bone density, geometry and strength in a cohort of chronic SCI participants.

Methods and analysis After meeting eligibility criteria and completing baseline testing, sixteen participants will be block randomised into the EAW alone group or the EAW+tSCS combined group (n=8 each group). Each group will receive a total of 108 overground training sessions (60 min sessions, 3 times a week, for 36 weeks) for the 9-month training period. Imaging for bone density and geometry by dual-energy X-ray absorptiometry and peripheral quantitative CT will be performed prior to starting the intervention (baseline), after 72 training sessions, and again after 108 sessions in each of the intervention arms. CT imaging of both lower extremities will be performed at baseline and at the 9-month time point in each of the intervention arms. Finite element models of bone loading will be generated based on three-dimensional (3D) reconstruction of bone architecture from CT imaging prior to and 9 months after the intervention.

Ethics and dissemination This study is currently approved by the Kessler Foundation and James J. Peters VA Medical Center Institutional Review Board. A member of the research team will review and explain the study consent form and will have all eligible participants sign prior to participation in the study. Results from this study will be disseminated to clinicians and researchers in the SCI community at national and international conferences.

Trial registration number NCT03096197.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The combination of exoskeletal-assisted walking (EAW)+transcutaneous spinal cord stimulation (tSCS) may promote a more reciprocal firing pattern for the flexors and extensors than EAW alone resulting in increased functional joint torque contribution of the lower limb.
⇒ This improved muscle activation pattern from tSCS could result in more normal mechanical forces on the lower extremity skeleton, greater ability to weight bear and ambulate, and a more appropriate stepping muscle activity as determined by electromyography.
⇒ The use of peripheral quantitative CT and CT-derived finite element model bone outcomes in this study may also improve the likelihood of detecting small changes in bone mineral density over time if an effect from either intervention arm exists.
⇒ The electrode stimulation configuration to optimise motor neuron pool excitement and maximise limb movement may not be understood and implemented in this study.
⇒ Correct identification of the vertebral body level by palpating the spinous process for electrode placement is limited due to soft tissue obstruction, hardware placement and fusion from surgery, as well as interparticipant differences in the number of thoracic and lumbar vertebrate.

BACKGROUND

Immobilisation, or an abnormal gait pattern, results in bone loss that predisposes individuals to osteoporosis and fracture, which can result in non-union, infection and deep venous thrombosis. There are approximately 305 000 individuals with spinal cord injury (SCI) in the USA, about 18 000 new cases each year,[1] and roughly 42 000 persons living with SCI are veterans.[2] Persons with

non-ambulatory SCI with greater loss of motor function undergo immediate unloading of the skeleton and, as a result, have marked loss of bone mineral density (BMD) below the level of lesion that is directly associated with increased risk of long-bone fractures. Histomorphometric studies of the sublesional skeleton early after SCI revealed an increase in osteoblast and osteoclast activity that shifts over months to an increase in osteoclastic activity and a suppression of osteoblastic activity.[3–5] This uncoupling of osteoblast/osteoclast function is supported by the clinical findings of hypercalciuria and dramatic elevation of biochemical markers of bone resorption,[6] leading to a rapid loss in BMD and deterioration of the trabecular lattice structure that is ultimately replaced by fatty marrow.[7] While it is appreciated that extreme demineralisation occurs throughout the entire lower extremity, the distal femur (DF) epiphysis and proximal tibia (PT) epiphysis are the regions most vulnerable to low-energy fracture in persons with SCI when performing activities of daily living.[8] Because a large proportion of accidents occur while sitting in a wheelchair, this makes the knee region the most common first anatomical point of contact with any externally applied force.

Although dual-energy X-ray absorptiometry (DXA) is the most affordable and accessible method to measure areal BMD (aBMD) at the DF and PT, peripheral quantitative CT (pQCT) is regarded as the more informative and sensitive method. The primary benefit of pQCT is it can measure volumetric BMD (vBMD) of the trabecular and cortical compartments of the DF, tibia and radius. Several studies have demonstrated vBMD is highly correlated with DXA-derived measures of aBMD,[9–11] and a history of fragility fracture in persons with chronic SCI.[12 13] Typical pQCT metrics are related to structural behaviour, and these biomarkers have been recommended for use as the primary outcome measurements in activity-based rehabilitation programmes and clinical trials that use pharmacological agents in persons with SCI.[14 15] There is considerable evidence that mathematical computation models are more effective than radiographic measurements to evaluate the mechanical competence of bone, which depends on geometry, mineral distribution, material properties and mode of loading.[16] The complex interactions among these parameters can be captured largely by subject-specific finite element (FE) modelling. CT-derived FE modelling has extensive use in the field of orthopaedic engineering[17] and allows for the computation of mechanical properties such as structural modulus, stress distribution, material tensile strength and compressive and torsional stiffness and strength. While DXA-derived aBMD explains approximately 50%–80% of the variability in bone strength,[18] FE-based metrics have captured between 10% and 40% greater variance in vertebral and femoral bone strength when compared with BMD alone.[19] In persons with SCI, FE-based metrics are better predictors of torsional stiffness and strength than metrics obtained by DXA and pQCT.[20] All these FE-based metrics have been well validated against cadaveric in vitro models of torsional stiffness and strength[20] and have been shown to be sensitive to small changes in bone strength over time.[21] Recent work by Edwards *et al*[22] and Morse *et al*[23] incorporated FE analysis methodology in clinical trials to evaluate the effects of the combined effect of pharmacological and mechanical interventions on bone strength after SCI, demonstrating the utility of FE models to calculate changes in bone strength in the clinical environment.

The clinical implications for rehabilitation professionals caring for persons with SCI and low BMD of the DF and PT are the potential risk of fracture from rehabilitation interventions that load the femur and tibia. A major challenge in the field has been to identify interventions that rebuild sublesional bone sufficiently to reduce the risk of sublesional fragility fractures. A few studies have investigated the effect of neuromuscular electrical stimulation (NMES) on bone formation/resorption in persons with SCI while loading in the standing position,[24] with additional reports demonstrating functional electrical stimulation (FES)-cycling or FES-rowing interventions increased bone density 6–9 months after beginning the study intervention. In a study by Lambach *et al*,[25] the authors reported that 90 sessions of an FES-rowing exercise programme, with each session lasting between 30 and 60 min over a period of 9–12 months, resulted in changes to bone that were proportional to the stimulus delivered. However, there is controversy regarding the ability of the typical FES cycle training programme (30 min sessions performed 3 times a week) to attenuate vBMD loss around the knee region in persons with SCI over the first year after traumatic motor-complete SCI,[26] and to rebuild bone in those with chronic SCI.[27 28] In a study of five participants with traumatic motor-complete SCI who completed exoskeletal-assisted walking (EAW) training three times per week, ≤60 min each session, for 6 weeks, Karelis *et al*[29] found a 14.5% increase in total vBMD at the distal tibia (DT) that trended towards significance (p=0.08). Other EAW studies found either no effect on BMD[30]—possibly because treatment duration was not long enough—or found a significant improvement in bone density but failed to control for multiple comparisons when performing the statistical analyses.[31]

Transcutaneous spinal cord stimulation (tSCS) neuromodulates the injured spinal cord by placing electrodes on the skin along the rostrocaudal axis of the lumbosacral segments to activate the central pattern generator to induce stepping patterns without supraspinal peripheral afferent input. The use of tSCS between the thoracic level-11 and level-12 and coccyx-level-1 has been shown to create rhythmic stepping-like movements with considerable electromyography (EMG) activity at the hamstrings, tibialis anterior (TA) and medial gastrocnemius (GN) muscles.[32] Previous work using tSCS has revealed low stimulation intensity may recruit lower threshold afferent fibres and motor axons, with increased recruitment as intensity of stimulation is increased.[33] Lumbosacral tSCS was applied at a frequency of 30 hz with an amplitude sufficient to produce acute lower extremity motor

responses in two men and one woman with motor-incomplete and sensory-incomplete chronic SCI (International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) neurological impairment grade D).[34] This stimulation combined with voluntary locomotor activity demonstrated immediate effects on motor output and kinematics with the most consistent finding in all participants being an increase of 11.3°±5.6° in the maximum hip angle during the swing phase.[34] In a recently published case series by Samejima *et al*,[35] two men with motor-incomplete and sensory-incomplete chronic SCI (ISNCSCI grade D) completed 2 months of cervical and lumbosacral tSCS with locomotor training (overground and manual assisted body weight support treadmill training) and 2 months of locomotor training alone; the 6 min walk test (6MWT) distance after 2 months of cervical and lumbosacral tSCS with locomotor training had a threefold greater distance compared with locomotor training alone.[35] In the study proposed here, we hypothesise that the greater reciprocal muscle-activation and a more normal gait pattern (ie, heal strike to toe-off-ground reaction forces) from this combined intervention would be anticipated to have a greater effect on bone remodelling at the total hip (TH), DF, PT, DT and calcaneus than that of EAW alone. If a significant increase in bone density, geometry and strength occurs from these interventions, the subject-specific FE modelling and advanced radiological measurement methodologies employed in this randomised controlled trial (RCT) could provide investigators the optimum approach to capture skeletal changes in the lower extremities.

Thus, three specific aims are being investigated in this study protocol. Aim 1: To compare the effect of EAW alone and EAW+tSCS combined on bone mineral content (BMC) and vBMD (mg/cm^3) at the DF after 6 and 9 months of each of the study interventions. Aim 2: To determine changes in pQCT-derived BMC, vBMD and geometry of the PT and DT; DXA-derived aBMD (g/cm^2) at the TH, DF, PT and calcaneus; and metrics of bone strength determined by FE modelling at the TH, DF, PT and calcaneus after 9 months of each of the study interventions. Aim 3: To determine the relationship between changes in bone density, geometry and strength to the change in motor capacity from EMG measurements of lower extremity muscles while stepping after 9 months of each of the study interventions.

METHODS

Study design

This study has been approved by the institutional review boards at the Kessler Foundation (KF) and the James J. Peters Veterans Affairs Medical Center (JJPVAMC). Subjects will be recruited to complete the bone outcomes from ongoing participants enrolled in the parent clinical that is investigating the effects of EAW alone or combined with tSCS compared with EAW alone on the changes in independent walking function, balance and lower extremity motor scores. For the parent study, after meeting study eligibility and completing baseline testing, participants are randomised into the EAW group or the EAW+tSCS group. The EAW group will receive 60 min of EAW overground training per session and the EAW+tSCS group will receive 60 min of EAW overground training with simultaneous lumbosacral tSCS per session, for a total of 108 sessions (3 times a week for 36 weeks). The study described here will capture DXA, pQCT and CT images prior to starting the intervention (baseline), after 72 training sessions (6-month time point), and again after 108 sessions (9-month time point) for participants in the EAW and EAW+tSCS arms. A no-intervention control group will not be studied over this study period because vBMD would remain unchanged or decrease in persons with chronic SCI, as determined from prior work.[36 37] To be able to perform FE modelling, CT imaging acquisition of both lower extremities is being obtained at baseline and at the 9-month time point in each of the intervention arms. Motion analysis and force data are also being collected at baseline and 9 months after beginning the study intervention. Surface EMG data will also be collected from muscles in each leg at medial bicep femoris (BF), rectus femoris (RF), vastus lateralis (VL), GN and TA muscles during 6MWT and 10MWT performed at baseline and 9 months after beginning the study intervention. The general study timeline and flow chart of screening, enrolment, interventions and assessments are presented in table 1 and figure 1.

Participant eligibility and recruitment

Sixteen eligible wheelchair-dependent chronic SCI participants are being enrolled and randomised and allocated to the EAW+tSCS combined group or an EAW alone group (8 participants/group). A complete list of inclusion and exclusion criteria used to identify potential study participants that apply to both the parent and substudy is presented (box 1). If potential participants meet the inclusion/exclusion criteria in the parent study, they qualify for participation in the substudy. Recruitment of participants is being conducted primarily through physician referral from the outpatient clinic at KIR and the National Institute on Disability, Independent Living and Rehabilitation Research SCI Model Systems database and referrals from the JJPVAMC SCI service physicians. Additional recruitment strategies include flyer distribution throughout the KF and JJP VAMC hospitals and through contacting prior study participants that have agreed to be contacted about future research when signing a notice of privacy practice. Over the course of the study, every effort is being made to include women and minorities in the study if eligibility criteria are met. Female participants of childbearing potential are being asked to complete a urine pregnancy test to ensure they are not pregnant prior to bone imaging at every time point. If the pregnancy test shows that a female participant is pregnant, or if female participants plan to become pregnant over the

Table 1 General study timeline of over the 3-year randomised controlled trial

	Year 1				Year 2				Year 3			
Research activities	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Institutional IRB approval	✓											
Recruitment (n=3 per quarter)		✓	✓	✓	✓							
Screen, enrol, randomise and allocate participants			✓	✓	✓	✓						
Study aims data collection				✓	✓	✓	✓	✓	✓			
Progress report				✓				✓				✓
Database entry and cleaning									✓	✓		
Statistical analysis and interpretation										✓	✓	
Dissemination and study closure												✓

✓, check mark indicates activity was compelted during the fiscal quarter specified
IRB, institutional review board; Q1, fiscal quarter 1; Q2, fiscal quarter 2; Q3, fiscal quarter 3; Q4, fiscal quarter 4.

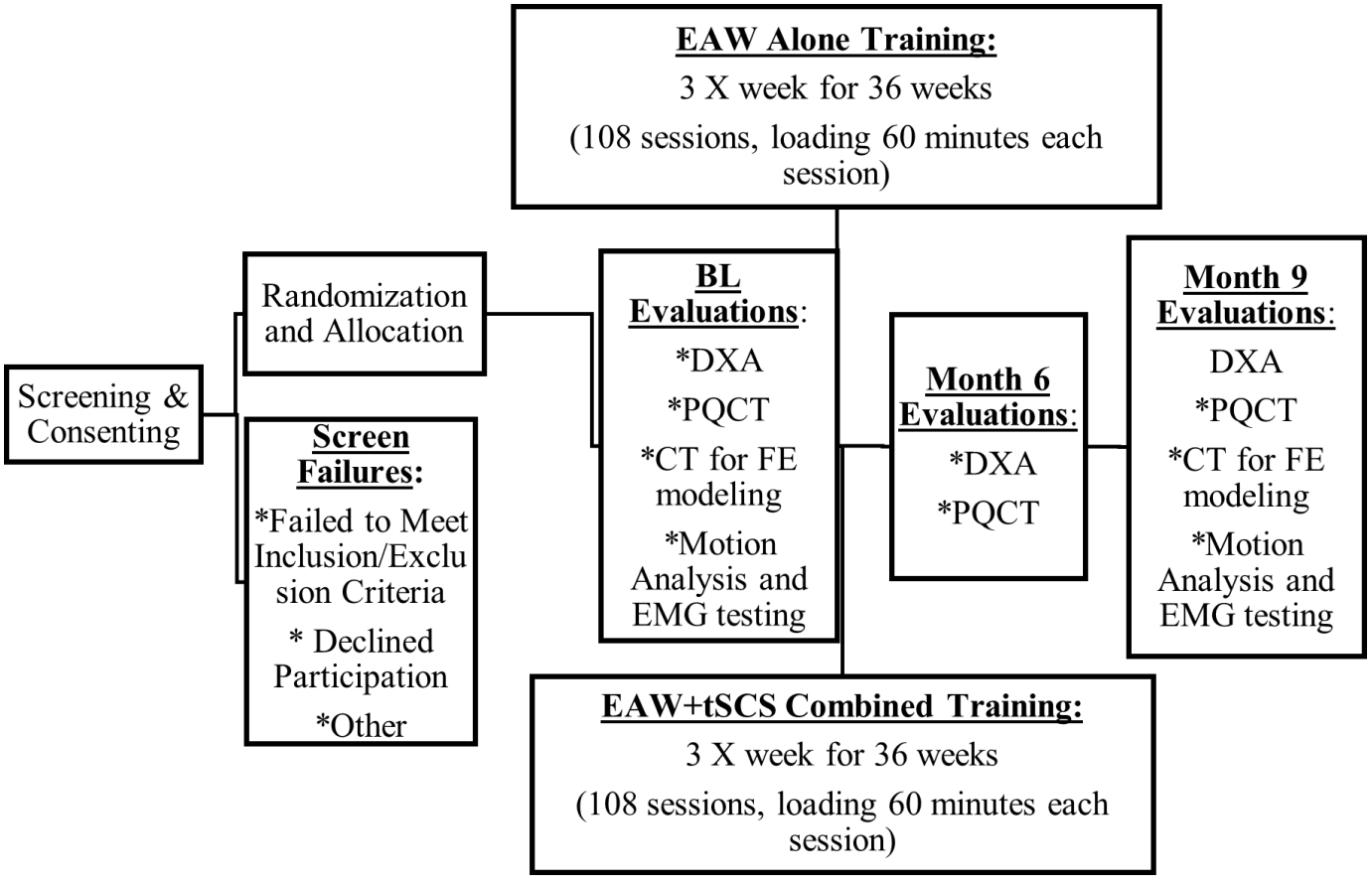

Figure 1 Study flow chart of screening, enrolment, interventions and assessments. DXA, dual-energy X-ray absorptiometry; EAW, exoskeletal-assisted walking; EMG, electromyography; FE, finite element; PQCT, peripheral quantitative CT; tSCS, transcutaneous spinal cord stimulation.

Box 1 Participant inclusion and exclusion criteria

Inclusion criteria

1. Adults between 21 and 58 years of age.
2. Non-walkers who are wheelchair reliant 100% of the time with an SCI greater than 6 months post injury.
3. As determined by the study staff, an ISNCSCI neurological impairment grade C (lower extremity motor score greater than or equal to 16) and grade D.
4. SCI at a neurological level of injury as determined by study staff between C5 and T10.
5. Anthropometric compatibility with the EAW device as follows: weight <220 lbs and height between 62 and 74 inches.
6. Capable of gripping Lofstrom crutches and/or walker without assistance.

Exclusion criteria

1. As determined by the study physician, a history of fragility fractured in the bones of the lower extremity that would put participants at increased risk of fragility fracture from the study intervention.
2. History of bone disease other than SCI related bone loss.
3. Positive pregnancy test or female participants who make plans to become pregnant over the course of the study.
4. Currently participating in a physical or occupational therapy programme.
5. Results from the baseline DXA study reveal a knee bone mineral density less than 0.60 gm/cm^2.

DXA, dual-energy X-ray absorptiometry; EAW, exoskeletal-assisted walking; ISNCSCI, International Standards for Neurological Classification of Spinal Cord Injury; SCI, spinal cord injury.

course of the study, they will be excluded or withdrawn (if already enrolled) from participation.

Consenting and randomisation

A member of the research team will review and explain the consent form and discuss the purpose of the study, procedures, risks/discomforts, and benefits with potential participants, and family members at the participant's request, prior to enrolment and answer any questions participants may have about the study. A copy of the signed consent form will be given to each participant and will be uploaded into the patient electronic health record. If participants agree to enrol in the study, the team member will have them summarise the purpose of the study and explain the study in layperson's terms to ensure they understand all procedures. If participants agree to be enrolled in the study, the team member will have them summarise the purpose of the study to ensure they understand all procedures and the PI will go over the study procedures again to identify potential obstacles or questions an individual may have. Participants' age, height, weight (computed body mass index), time since injury and level of injury (paraplegia or tetraplegia) will be recorded. In addition to this demographic information, level of injury and lower extremity motor score will be obtained using the ISNCSCI scale for neurological impairment obtained in the parent study. Records will be kept confidential by removing the names of the participants from all data and assigning each participant a random identification number that will be recorded on all participant data sheets and linked by identifiers to a master key that is appropriately secured behind a firewall. A computer-generated schedule using eight blocks randomised in a 1:1 manner via an online research randomizer (www.randomizer.org) will be used to randomise participants to the two groups. This will be done prior to beginning the study by research personnel who are not affiliated with the study protocol in any other manner. The randomly generated identification number will be used on all paper and electronic data records for the study and will be stored in a locked cabinet and a designated firewall.

Patient and/or public involvement

Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

Trial status

The parent RCT started study enrolment in March 2017 with the substudy starting enrolment in January 2023. The completion date for both the parent RCT and substudy is scheduled for September 2025. The parent study was approved by institutional review board (IRB) at the KF (protocol # D-927-16) in February 2017 with the substudy approved by the KF IRB in May 2022 and by the JJPVAMC IRB (protocol # 1689800) and R&D in June 2022.

Study interventions

EAW training

The robotic exoskeleton manufacturer's operating manual (EksoNR, Ekso Bionics, Richmond, California, USA) will be used to determine settings and training principles for this study that have been previously implemented by our group.[38] Anthropometric measurements will be used to fit the Ekso to each individual to the device and hip and ankle adjustments made to accommodate the participants range of motion. The study physical therapists will perform the fitting evaluation. All EAW training will be completed with the use of an assistive walking device (forearm crutches or rolling walker). Based on the settings and guidelines, step initiation will be performed using either the 'First Step' (therapist controls each step), 'ProStep' (participant initiates each step based on achieving trunk forward and lateral lean targets) or 'ProStep+' (participant initiates each step based on trunk lateral lean target and trailing leg lifted) settings according to the individual's ability to effectively initiate stepping. Training will be progressed for each individual to optimise independent walking by using different trajectory swing assist modes. The swing assist settings available with the EksoNR include the 'max assist (MA)', 'adaptive assist (AA)' and 'fixed assist (FA)' modes. The MA provides 100% of the Ekso motor power that is constant throughout the swing phase trajectory while the FA provides a ceiling amount of motor power up to the preprogrammed percentage of the maximum

motor power (0%–100%). To assist participants to achieve the maximum number of steps over the course of the training programme, the AA mode will be adjusted to the participant's EAW skills to provide the assistance needed to complete a step successfully. Feedback scores will be provided to the participants with the full amount of motor assistance contributing to a step when the score is one hundred, with the feedback scores reduced as the participant contributes more assistance when completing a step. The EAW alone group will also receive 60 min of EAW overground training per session, 3 times a week for 36 weeks, for a total of 108 sessions, over the 9-month training programme.

EAW+tSCS training

Participants will perform EAW training while tSCS is delivered simultaneously using the same EAW procedures described in the previous section (EAW Training). Prior to beginning every EAW+tSCS combined training session, participants' skin will be checked for signs of breakdown, redness and scabbing. A picture will be taken before and after every session for comparison and to check if signs of skin irritation occur at any session over the training period. Lumbosacral tSCS will be delivered by placement of a rectangular 1.5×3.5 inch cathode electrode (Axelgaard, ValuTrode Cloth, Axelgaard Manufacturing, Fallbrook, California, USA) at the interspinous process at the T11–T12 verterbral level for proximal leg muscle recruitment and the L1–L2 or coccyx-1 vertebral level for distal leg muscle recruitment.[39–41] Annode electrodes (Axelgaard, ValuTrode Cloth, Axelgaard Manufacturing) will be symmetrically placed at the anterior–superior iliac crests (common ground) to enable the greatest synergistic effect to be obtained and will be assessed by EMG during active stepping in both intervention groups. A tSCS customised stimulation unit consisting of a Texas Instruments Class-D amplifier (TAS5825P) in voltage mode, and a 12:1 step-up transformer (Xicon 42TM003-RC) will be used to deliver a biphasic waveform. A range of stimulation amplitudes (1–200 mA), frequencies (5–60 Hz) and pulse durations (0.1–1 ms) will be used to optimise stimulation parameters for each individual using a carrier frequency of 10 kHz. However, based on previous reports,[32 41 42] stimulation configuration will vary between participants to ensure the stimulating electrodes deliver a uniform electrical current that excites multiple motor neurons to achieve appropriate limb movement. The same EAW procedures described in the previous section will be followed when delivering tSCS during the EAW training. The EAW+tSCS group will receive 60 min of robotic intervention training per session, 3 times a week for 36 weeks, for a total of 108 sessions, over the 9-month training programme. Based on previous research in the Centre for Spinal Stimulation, 60 sessions of activity-based training have been shown to be efficacious for recovery of walking after SCI.[43 44]

Assessments

Measurements of bone density, geometry and strength will be performed using DXA, pQCT and CT imaging at baseline and again 9 months after beginning the study intervention, with an additional DXA and pQCT assessment done 6 months after beginning the study intervention. In addition, three-dimensional motion analysis and EMG muscle activation testing will be obtained during a 6 MWT and 10 MWT at baseline and again 9 months after beginning the study intervention. If participants voluntarily discontinue study participation or are withdrawn from the study over safety concerns, a best effort will be made to complete all the assessments and usethem for 6-month and 9-month endpoints if possible. The following bone measurement outcomes will be performed and analysed by a single International Society for Clinical Densitometry (ISCD) certified bone densitometry technician blinded to participant assignment. The bone metrics that can be obtained using DXA, pQCT and CT imaging are summarised in a guideline entitled 'Bone Health and Osteoporosis Management in Individuals with SCI, Clinical Practice Guideline for Health Care Providers' and is available for download at the Paralyzed Veterans of America website (www.pva.org/publications).

DXA scanning

Bilateral TH, DF, PT (epiphysis and metaphysis) and calcaneal aBMD values will be obtained using a DXA densitometer (iDXA, General Electric, Madison, Wisconsin, USA). Dedicated technicians who are certified by the ISCD will acquire DXA images with a participant lying on a padded tabletop. The knee software acquisition and analysis method has been validated against QCT in persons with SCI[11] and has been used previously by our group to monitor changes in BMD at the knee in an RCT investigating the effect of a pharmacological agent to preserve BMD in persons with subacute SCI.[45 46] The calcaneus will also be obtained using an investigator-generated protocol that has demonstrated excellent reliability in persons with SCI.[47] As per the ISCD guidelines, the least significant change (LSC) is required to be reported when performing serial DXA scans.[48] The ongoing LSC aquired in our lab on 30 SCI participants using the 'on-and-off-the-table' method (ie, subjects were repositioned between scans), yielded the following values for LSC–coefficient of variation (CV%): TH=3.0%, DF=3.5% and PT=5.0%0.[45]

pQCT scanning

A Stratec XCT 3000 densitometer (STIM designs, Carmel, California, USA) will be used to perform pQCT measurements of the DF, PT and DT. To optimise the reliability of the serial scan pQCT slices, a scout view will be first performed to allow the positioning of cross-sectional measurements along the tibia moving distal to proximal, with the measurement beginning at the reference line that was placed at the tibiofemoral joint for the femur slice and the talocrural joint for the tibia scans. Measurement of BMC and vBMD will be made at the epiphysial

region at the 4% femoral length proximal to the knee joint (DF); four additional tibial sites will be obtained by imaging proximal (eg, superior ankle joint) to distal of the tibial length: 4% (DT), 38% and 66% for cortical vBMD, and the 96% (PT). Slice thickness of 2.4 mm and default voxel size of 0.5 mm will be acquired, as previously described.[49 50] The root mean square-CV (RMS-CV%) for pQCT is 1%–2.3% for vBMD, trabecular vBMD and geometric measures at the DF.[15] The trabecular or cortical BMC (mg) and vBMD (mg/cm^3) variables and the associated geometry variables cortical area (mm^2), cortical thickness (mm), polar moment of inertia (mm^4) and the stress-strain index (mm^3) will be obtained at the respective slices, as previously defined.[15 51]

CT scanning

Bilateral TH, DF, PT and calcaneus regions will be obtained in a clinical CT scanner (Siemens Somatom Definition AS). The volumetric CT scans will be used to acquire radiography-based bone metrics as well as serve as input for subject-specific FE models to determine bone stiffness and strength. The CT scan parameters are peak KV=120 kVp, X-ray tube current=280 mA, exposure time=1000 ms, focal spot(s)=1.2 and 'Smart Scan' parameter CareDose4D turned off. A participant will be positioned in an anatomically neutral position simulating upright standing. The feet may need to be dorsiflexed with the help of straps held by the participant during scanning. Calibration (hydroxyapatite with different densities representing bone in water-equivalent background, lenite polyethylene representing bone in fat-equivalent background) rods will be taped onto the feet prior to scanning. The raw CT data will be used to reconstruct stacks of images in the sagittal, axial and coronal planes, with in-plane resolution of 0.36×0.36 mm and slice thickness of 0.6 mm, which provides ample resolution to determine compositional properties of bone by FE modelling.

FE modelling for quantifying bone mechanical competence

Subject-specific FE modelling will be used to determine bone mechanical competence, namely compressive and torsional stiffness and strength, at the TH, DF, PT and calcaneus. A framework will be implemented using custom Python scripting and includes the following steps:

Image segmentation: The programme 3D slicer will be used to manually segment the bones from the CT scans at the hip, DF, PT and the calcaneus.

Geomagic: The surface geometry will be inspected and modified to produce clean smooth NURBS surfaces from the segments using Geomagic.

Meshing: The 3D geometries obtained from image segmentation will be meshed automatically using tcl scripting in Hypermesh (Altair Engineering, Troy, Michigan USA).

The bones will be represented as tetrahedral elements and have regions of interest (ROI) for FE analyses and subsequent postprocessing. Based on a prior convergence study[16] and internal review, tetrahedral elements with an average edge length of 2 mm were found to be comparably sufficient.

Material properties

Bone material properties will be assigned using 3D Slicer, Bonemat[52] and custom Python scripting. Calibration phantoms and their mean Hounsfield units (HU) (greyscale) will be extracted through a voxel-by-voxel approach from CT images to bone density in 3D Slicer. A linear relationship is generated between the hydroxyapatite densities and the HU values of the calibration phantoms. In Bonemat and with custom Python scripting, bone elements will be defined as linear orthotropic,[21] with elastic moduli in the axial direction E3 defined using an established relationship.[53]

Boundary conditions: The FE models will be set up in Abaqus (SIMULIA, Providence, Rhode Island, USA) using custom Python scripting. Each bone will be subjected to a torsional (internal rotation) displacement.[21] The surface nodes of the cut end of a bone will be fixed. The displacements will be applied to a reference node placed at the geometric centre of the free end of the bone. This reference node will be kinematically coupled to the nodes at the free end. All other df of the reference node will be constrained.

FE simulations: The FE models will be run in Abaqus.

Postprocessing: Custom Python scripts will be developed to extract the reaction force and torque results from the FE simulations. These data will be used to calculate bone stiffness and strength.[20 21]

From this CT-derived FE model, the primary bone strength biomarkers torsional stiffness (K) and torsional strength (T_{ult}) will be calculated. A preliminary model of the PT generated by the study engineers (SP and WK) has been provided (figure 2).

Motion analysis and EMG muscle activation: 6MWT and 10MWT

A standard 6MWT and 10MWT will be completed when participants are proficient enough at EAW and can minimise the number of pauses when stepping. Both tests will be performed while obtaining 3D motion analysis and 16-channel surface EMG during a single experimental session. Both tests are being performed in the KF research laboratory with the distance travelled during the 6MWT recorded using a distance measuring wheel and the time to complete the 10MWT will also be obtained using a standard stopwatch. A 12-camera motion analysis (sampled at 60 Hz) study will collect positional data over 6–10 gait cycles for 3D kinematics at the hip, knee and ankle during standing and walking overground. Retroreflective markers will be placed on each subject and exoskeleton to capture the position and orientation of all the interconnected body/exoskeleton segments. The marker trajectories will be synchronised with ground reaction force (Bertec, Columbus, Ohio, USA) and insole pressure (Tekscan, Boston, Massachusetts, USA) data. Tekscan F-scan Versatek foot pressure sensor system will

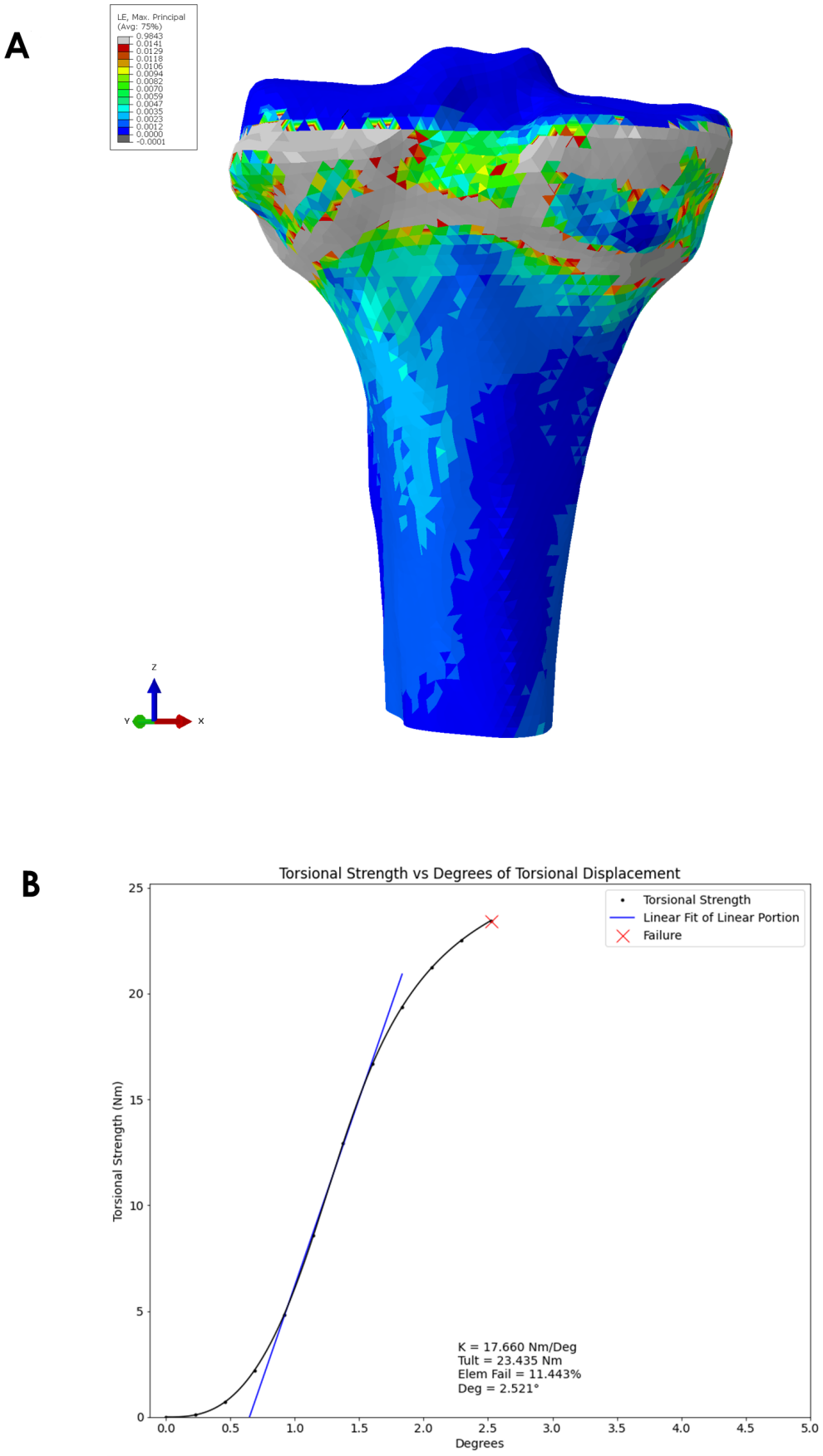

Figure 2 Image of bone strain mapping at the (A) proximal tibia from the QCT-derived FE model and the corresponding graph of the (B) torsional strength versus degrees of torsional displacement and the metrics of torsional stiffness (K) and torsional strength (T_{ult}). FE, finite element; QCT, quantitative CT.

measure forces (sampled at 100 Hz) under the subject's feet when walking in the exoskeleton device in the two intervention arms. The Versatek is wireless and has data logging capabilities, negating the need to tether the participants for data collection. These data will allow us to collect normalised loading force for those individuals who have difficulty stepping or walking in the device. Using a 16-channel Motion Lab System (Motion Lab Systems, Baton Rouge, Los Angeles, USA) surface EMG will be collected to measure muscle activations during the walking tests placing electrodes on the BF, GN, S, RF, VL and TA muscles in each leg. Signal band frequencies range between 10 and 600 Hz and sampling rate of 10 000 Hz. Kinematics, ground reaction force, insole pressure and EMG data will be used to create participant-specific FE models in addition to simulated FE models.

Statistical analyses

Results will be expressed as group estimated marginal means, SD and 95% CIs, where applicable. At all study time points, continuous variables will be tested for a normal distribution using the Shapiro-Wilk test. Furthermore, kurtosis and skewness will also be calculated to determine if they were within the ±1.96 SD threshold. Additional visual inspection of histograms, boxplots, normal Q-Q plots were also performed to identify potential outliers and to rule out the possibility of database entry errors. Independent t-tests will be performed on baseline values to identify group (EAW+tSCS vs EAW) differences for demographic clinical characteristics and bone biomarkers (bone density, geometry and strength values). To identify changes across the 6-month and 9-month time points, at the respective ROI, all continuous bone density (aBMD, BMC, total vBMD, trabecular BMC, trabecular vBMD, cortical BMC, cortical vBMD (mg/cm^3)) and geometry (cortical area, cortical thickness, polar moment of inertia and stress-strain index) values will be compared using a 3×2 (time×treatment group) hierarchical linear mixed-model analysis. To identify change at the 9-month time point, continuous values for strength (compressive and torsional stiffness and strength) from the FE modelling will be compared using a separate 2×2 hierarchical linear mixed-model analysis. To control for dependencies within the dataset, the models will be adjusted for random slopes and intercepts using age, duration of SCI and lower extremity motor as covariates. To further characterise significant within-group differences from BL at various time points, post hoc pairwise comparisons will be performed using a Bonferroni correction to control for the type-I error rate from multiple comparisons. From the mixed-model analyses, effect sizes and corresponding 95% CIs will be determined. Correlation coefficients from a correlation matrix of the difference scores between EMG muscle activity and bone density, geometry, and strength value difference scores will be determined. Significant relationships will be further explored by regression analyses to determine the predictability of the change in muscle activity by EMG and the difference in 6-month and 9-month bone biomarker values.

Table 2 Sample size/power calculations

ANOVA-repeated measures within and between interactions	vBMD distal femur
Test significance level, α	0.05
Two-sided test	2
Effect size	0.78
Power (%)	99
n per group	8
Power (%), with 25% attrition rate	90
n per group, with 25% attrition rate	6

ANOVA, analysis of variance; vBMD, volumetric bone mineral density; α, alpha.

Power analysis

It was necessary to use the effect of powered EAW alone in persons with chronic motor-complete SCI to calculate the effect size for our proposed work because at the time of initiation of this work vBMD data from the combined EAW+tSCS intervention was not available. In the study by Karelis *et al*,[29] in five motor-incomplete participants (ISNCSCI grade D), there was an increase in vBMD of 14.5%±11.2% (p=0.08) at the mid-tibia region after 6 weeks of powered EAW training, performed three times a week, for up to 60 minutes each session. As such, the longer training protocols in this proposal (3 times a week for 36 weeks, for up to 60 minutes each session), in both the EAW alone and the EAW+tSCS arms, would be anticipated to have no less than the same per cent increase in vBMD at the DF. Using an alpha of 0.05 and an effect size of 0.78 calculated from the mean difference in vBMD reported by Karelis *et al*,[29] an initial sample size of 8 study participants per group would yield a power of 99% (G*Power[54] V.3.0.1.0, Franz Faul, Universit€at, Kiel, Germany). With a hypothesised attrition rate of 25% per group and an alpha of 0.05, the projected sample size of 6 study participants per group in the proposed study will yield a power of 90%. Complete results from the power calculation have been provided (table 2).

Potential risks and discomforts

Bone density studies

There is minimal discomfort associated with the bone density studies (DXA, pQCT and CT). Participants will be asked to transfer or be transferred by appropriate staff from their wheelchair to the densitometer table top. Bone density studies are associated with a small risk from radiation; the total amount of radiation exposure from the DXA and pQCT will be no greater than 287 µSv at the Baseline and 9 month time points (less than 5 routine chest X-ray (PA film, ~60 µSv)) and no greater than 27 µSv at the 6-month time point (1/4 of the effective dose

received from a routine chest X-ray). The radiation exposure from the CT scan at the baseline and 9 month timepoint will be approximately 250 mSv of radiation over a 5 second period. This radiation dose is equivalent to 30 times the radiation exposure from a normal chest x-ray. At each time point, female participants of childbearing potential will be asked to complete a urine pregnancy test to ensure they are not pregnant prior to bone imaging. If the pregnancy test shows that female participants are pregnant, then they will be withdrawn from the study.

EAW and EAW+tSCS interventions

In participants who are performing stepping exercises in the EAW+tSCS or EAW arms of the study, there is a risk of increased breathing, shortness of breath or dizziness. If participants experience any chest pain or irregular heartbeats during stepping, the stepping will be terminated and the study physician will immediately be informed. From both the EAW+tSCS and EAW arms of the study, participants may experience muscle and joint aches, joint sprains and fractures (the risk of a fracture is small, but it is important to appreciate that bone fracture remains a potential risk). During the tSCS of the lower back, participants may experience tingling in their legs. There is also the risk of headaches, autonomic dsyreflexia, skin breakdown at the electrode placement site, pain, muscle spasms and muscle tears. If any of these potential risks occur, the stimulation will cease immediately, and the investigators will closely monitor the participant until symptoms resolve. Participants may experience skin abrasion or bruising due to rubbing of the harness to support the body weight or due to manual contact to the lower limbs or due to braces worn on the lower limbs. After the electrodes are removed, the adhesive may cause skin irritation and temporary skin discolouration. Sudden increase or decrease in blood pressure (BP) may occur during training and/or testing. Before each training session, BP will be evaluated (three consecutive BP measurements) and taken continuously during the training, and if a participant's BP drops below the limit recommended by the examining clinician, or if the participant complains of dizziness, light-headedness, nausea or vomiting symptoms, they will rest seated with their feet elevated. After 5 min of rest and return to baseline conditions, the participant may resume standing and BP and signs of symptoms will continue to be monitored. If the participant cannot tolerate training for 60 min because BP consistently drops, they will stop for that session and training time will be recorded for future analysis. The most severe risk associated with EAW is falling. To help minimise falls, physical therapists who are highly experienced in gait training with braces and EAW training in persons with SCI (Ekso trained and certified) will perform the training sessions with all participants. The physical therapists will guard study participants to assist with balance perturbations while standing or walking to help prevent falls. Other possible risks from EAW include discomfort, triggered spasm, reflex bowel or bladder activity, or skin pressure/friction. If participants experience injury, discomfort, excessive spasms, incontinence, refractory or repeated hypotension or any other ensuing medical condition deemed as a disqualifier by Kessler Research Staff, the participant will be terminated from the study.

Data and safety monitoring

Paper data with identifying information will be kept on-site in locked cabinets, behind double locked doors. Digital data will be stored in a password-protected database and maintained on the network behind a designated firewall. Participants will be rigorously monitored during the training sessions with the study team contacting participants on days they are not training to ensure there are no delayed or carryover effects from the study interventions. If problems with study interventions and/or procedures are reported by participants over the course of the study, the protocol may be modified by completing an IRB amendment. Any change in medical history will be evaluated by the study team and the participants' SCI physician. An adverse event status will be determined based on the IRB of records criteria for adverse event reporting. All severe and serious adverse events will be submitted to the IRB within a 48-hour period regardless of relationship to the study intervention. From this adverse event monitoring, an emerging treatment adverse event table will be reported at the time of publication. To ensure compliance with this data and safety monitoring plan, this study will be audited every year.

DISCUSSION

Rehabilitation professionals caring for persons with SCI and low BMD of the DF and PT should have a heightened appreciation of the potential risk of fracture from prescribing gait rehabilitation interventions. There are limited rehabilitation options currently available to clinicians for the treatment of sublesional osteoporosis and fracture prevention in the chronic SCI population. The use of NMES and FES has been minimally effective to increase lower extremity long-bone BMD in individuals with chronic SCI,[24 27] and the effect on bone preservation is rapidly lost when NMES or FES training is reduced or terminated.[55 56] We hypothesise the combination of EAW+tSCS will promote a more reciprocal firing pattern for the flexors and extensors than EAW alone resulting in increased functional joint torque contribution of the lower limb. This improved muscle activation pattern from tSCS could result in more normal mechanical forces on the lower extremity skeleton, greater ability to weight bear and ambulate, and a more appropriate stepping muscle activity as determined by EMG. The use of pQCT and CT-derived FE model bone outcomes in this study may also improve the likelihood of detecting small changes in BMD over time if an effect from either intervention arm exists.

The study outlined here presents the details of a RCT that will test a potential clinical option for the treatment

of sublesional osteoporosis in individuals with chronic SCI that could potentially have a profound beneficial impact on a person's quality of life. Restoration of sublesional bone in persons with SCI would reduce the morbidity and days lost from work associated with fractures, a known secondary complication that often results in profound and prolonged immobilisation. Higher bone mass and an assumed greater load-bearing ability of bones in paralysed regions would increase the numbers of persons with SCI who are eligible for activity-based rehabilitation strategies, such as electrical stimulation and ambulation in exoskeletal systems. Improvements in sublesional bone would also improve confidence to engage in personal activities (recreational endeavours, independence and ease in which one performs activities of daily living) and quality of life because of the ability to engage more securely and confidently in social activities and to more fully integrate into the community. A long-term outcome of improving sublesional bone health in persons with SCI is that future neuroregenerative strategies to improve neurological function will have a lower risk of fragility fractures when weight-bearing activities or walking are performed.

Limitations

The methodology for optimum stimulation configuration when performing tSCS is still evolving. The stimulation configuration to optimise motor neuron pool excitement and maximise limb movement may not be implemented in this study. Future reports will use improved methodologies that manipulate electrode size and vertebral placement, stimulation frequency, waveform configurations and minimise subjective reports of paresthesia to optimally induce a spinally evoked motor response. Correct identification of the vertebral body level by palpating the spinous process for electrode placement is limited due to soft tissue obstruction, hardware placement and fusion from surgery, as well as interparticipant differences in the number of thoracic and lumbar vertebrates. To understand the accuracy of electrode placement, future studies are needed to validate surface landmarks against DXA lateral vertebral scans or other advanced radiological techniques. It is possible that the BMD outcomes will be improved from baseline in both intervention groups and/or the effect is observed only in individuals who have the highest BMD values at baseline due to their greater structural bone integrity. Finally, the investigators do not have a plan in place to perform a cost-effective analysis, making it difficult to understand the external generalisability of our findings.

Ethics and dissemination

The experimental protocol is registered on ClinicalTrials.gov (NCT03096197). This study is currently approved by the KF and JJPVAMC IRB. A member of the research team will review and explain the study consent form and will have all eligible participants sign the consent form prior to participation in the study. Dissemination of preliminary findings for use by other groups will be completed when enough participants have been completed so a representative case series can be reported. Results from this study will be disseminated to clinicians and researchers in the SCI community at national and international conferences via the American Spinal Cord Injury Association, International Spinal Cord Society and the International Society for Clinical Densitometry. Furthermore, we anticipate that the observations made in this study will be published in peer-reviewed journals, including those in the field of Spinal Cord Medicine (ie, *Journal of Spinal Cord Medicine*, *Archives of Physical Medicine and Rehabilitation*, *Spinal Cord*, etc) and osteoporosis and bone measurement journals (ie, *Osteoporosis International*, *Journal of Clinical Densitometry*, etc). Information will be delivered to the SCI community using VA, KF, Paralyzed Veterans of America, New Jersey Institute of Technology and the Icahn School of Medicine at Mount Sinai periodic newsletters and internet blogs.

Author affiliations
[1]Spinal Cord Damage Research Center, James J. Peters VA Medical Center, Bronx, NY, USA
[2]Department of Physical Medicine and Rehabilitation, Rutgers New Jersey Medical School, New Brunswick, NJ, USA
[3]Department of Biomedical Engineering, New Jersey Institute for Technology, Newark, NJ, USA
[4]Center for Spinal Stimulation and Center for Mobility and Rehabilitation Engineering, Kessler Foundation, West Orange, NJ, USA
[5]Departments of Medicine and Rehabilitation and Human Performance, Icahn School of Medicine at Mount Sinai, New York, NY, USA
[6]Department of Interdisciplinary Studies, School of Health Professions, Rutgers Biomedical and Health Sciences, Newark, NJ, USA
[7]Biomedical Engineering, New Jersey Institute of Technology, Newark, NJ, USA

Acknowledgements The authors would like to thank the ongoing and future study participants with spinal cord injured for volunteering their time to this study.

Contributors All of the authors on this study contributed to the protocol presented. CMC, WAB, JSP, GF and AMS contributed to study design; CMC, GF and CC contributed to study conduct and data collection; WK and SP contributed to development of the FE model; JSP and AMS contributed to statistical and power analysis; CMC drafted the initial draft of the manuscript; and all authors read, edited and approved the submitted version of Manuscript. The first and corresponding author CMC is the guarantor.

Funding This study is being supported by the National Institute on Disability, Independent Living and Rehabilitation Research (NIDILRR, grant # 90RE5021-01-00), The Tim and Caroline Reynolds Foundation (grant # 0046) and the Department of Veterans Affairs, Veterans Health Administration, Rehabilitation Research & Development Service Career Development Award-1 (Grant # 5IK1RX003974-02, Project # B3974-M) and Merit Review (Grant # #1 I01 RX003561).

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iD
Christopher M Cirnigliaro http://orcid.org/0000-0003-1929-5067

REFERENCES

1 National Spinal Cord Injury Statistical Center. *Facts and figures at a glance*. Brimingham, Alabama: University of Alabama at Birmingham, 2024.
2 DVA. Research on spinal cord injury. 2024. Available: https://www.research.va.gov/topics/sci.cfm
3 Bauman WA, Cardozo CP. Osteoporosis in individuals with spinal cord injury. *PM R* 2015;7:188–201.
4 Minaire P, Neunier P, Edouard C, *et al*. Quantitative histological data on disuse osteoporosis: comparison with biological data. *Calcif Tissue Res* 1974;17:57–73.
5 Chantraine A, Nusgens B, Lapiere CM. Bone remodeling during the development of osteoporosis in paraplegia. *Calcif Tissue Int* 1986;38:323–7.
6 Roberts D, Lee W, Cuneo RC, *et al*. Longitudinal study of bone turnover after acute spinal cord injury. *J Clin Endocrinol Metab* 1998;83:415–22.
7 Shields RK, Dudley-Javoroski S, Boaldin KM, *et al*. Peripheral quantitative computed tomography: measurement sensitivity in persons with and without spinal cord injury. *Arch Phys Med Rehabil* 2006;87:1376–81.
8 Morse LR, Lazzari AA, Battaglino R, *et al*. Dual energy x-ray absorptiometry of the distal femur may be more reliable than the proximal tibia in spinal cord injury. *Arch Phys Med Rehabil* 2009;90:827–31.
9 Xiaoguang C, Ling W, Qianqian W, *et al*. Validation of quantitative computed tomography-derived areal bone mineral density with dual energy X-ray absorptiometry in an elderly Chinese population. *Chin Med J* 2014;127:1445–9.
10 Cann CE, Adams JE, Brown JK, *et al*. CTXA hip--an extension of classical DXA measurements using quantitative CT. *PLoS ONE* 2014;9:e91904.
11 McPherson JG, Edwards WB, Prasad A, *et al*. Dual energy X-ray absorptiometry of the knee in spinal cord injury: methodology and correlation with quantitative computed tomography. *Spinal Cord* 2014;52:821–5.
12 Lala D, Craven BC, Thabane L, *et al*. Exploring the determinants of fracture risk among individuals with spinal cord injury. *Osteoporos Int* 2014;25:177–85.
13 Eser P, Frotzler A, Zehnder Y, *et al*. Fracture threshold in the femur and tibia of people with spinal cord injury as determined by peripheral quantitative computed tomography. *Arch Phys Med Rehabil* 2005;86:498–504.
14 Troy KL, Morse LR. Measurement of Bone: Diagnosis of SCI-Induced Osteoporosis and Fracture Risk Prediction. *Top Spinal Cord Inj Rehabil* 2015;21:267–74.
15 Cervinka T, Giangregorio L, Sievanen H, *et al*. Peripheral Quantitative Computed Tomography: Review of Evidence and Recommendations for Image Acquisition, Analysis, and Reporting, Among Individuals With Neurological Impairment. *J Clin Densitom* 2018;21:563–82.
16 Campbell GM, Glüer C-C. Skeletal assessment with finite element analysis: relevance, pitfalls and interpretation. *Curr Opin Rheumatol* 2017;29:402–9.
17 Goel VK, Nyman E. Computational Modeling and Finite Element Analysis. *Spine (Phila Pa 1976)* 2016;41 Suppl 7:S6–7.
18 Ammann P, Rizzoli R. Bone strength and its determinants. *Osteoporos Int* 2003;14 Suppl 3:S13–8.
19 Dall'Ara E, Schmidt R, Pahr D, *et al*. A nonlinear finite element model validation study based on a novel experimental technique for inducing anterior wedge-shape fractures in human vertebral bodies in vitro. *J Biomech* 2010;43:2374–80.
20 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.
21 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.
22 Edwards WB, Simonian N, Haider IT, *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;33:1729–40.
23 Morse LR, Troy KL, Fang Y, *et al*. Combination Therapy With Zoledronic Acid and FES-Row Training Mitigates Bone Loss in Paralyzed Legs: Results of a Randomized Comparative Clinical Trial. *JBMR Plus* 2019;3:e10167.
24 Dudley-Javoroski S, Saha PK, Liang G, *et al*. High dose compressive loads attenuate bone mineral loss in humans with spinal cord injury. *Osteoporos Int* 2012;23:2335–46.
25 Lambach RL, Stafford NE, Kolesar JA, *et al*. Bone changes in the lower limbs from participation in an FES rowing exercise program implemented within two years after traumatic spinal cord injury. *J Spinal Cord Med* 2020;43:306–14.
26 Eser P, de Bruin ED, Telley I, *et al*. Effect of electrical stimulation-induced cycling on bone mineral density in spinal cord-injured patients. *Eur J Clin Invest* 2003;33:412–9.
27 Bélanger M, Stein RB, Wheeler GD, *et al*. Electrical stimulation: can it increase muscle strength and reverse osteopenia in spinal cord injured individuals? *Arch Phys Med Rehabil* 2000;81:1090–8.
28 Dudley-Javoroski S, Shields RK. Regional cortical and trabecular bone loss after spinal cord injury. *J Rehabil Res Dev* 2012;49:1365–76.
29 Karelis AD, Carvalho LP, Castillo MJ, *et al*. Effect on body composition and bone mineral density of walking with a robotic exoskeleton in adults with chronic spinal cord injury. *J Rehabil Med* 2017;49:84–7.
30 Kim HS, Park JH, Lee HS, *et al*. Effects of Wearable Powered Exoskeletal Training on Functional Mobility, Physiological Health and Quality of Life in Non-ambulatory Spinal Cord Injury Patients. *J Korean Med Sci* 2021;36:e80.
31 Bass A, Morin SN, Guidea M, *et al*. Potential Effects of an Exoskeleton-Assisted Overground Walking Program for Individuals With Spinal Cord Injury Who Uses a Wheelchair on Imaging and Serum Markers of Bone Strength: Pre-Post Study. *JMIR Rehabil Assist Technol* 2024;11:e53084.
32 Gerasimenko Y, Gorodnichev R, Moshonkina T, *et al*. Transcutaneous electrical spinal-cord stimulation in humans. *Ann Phys Rehabil Med* 2015;58:225–31.
33 Minassian K, Persy I, Rattay F, *et al*. Posterior root-muscle reflexes elicited by transcutaneous stimulation of the human lumbosacral cord. *Muscle Nerve* 2007;35:327–36.
34 Hofstoetter US, Krenn M, Danner SM, *et al*. Augmentation of Voluntary Locomotor Activity by Transcutaneous Spinal Cord Stimulation in Motor-Incomplete Spinal Cord-Injured Individuals. *Artif Organs* 2015;39:E176–86.
35 Samejima S, Caskey CD, Inanici F, *et al*. Multisite Transcutaneous Spinal Stimulation for Walking and Autonomic Recovery in Motor-Incomplete Tetraplegia: A Single-Subject Design. *Phys Ther* 2022;102:pzab228.
36 Frey-Rindova P, de Bruin ED, Stüssi E, *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;38:26–32.
37 de Bruin ED, Dietz V, Dambacher MA, *et al*. Longitudinal changes in bone in men with spinal cord injury. *Clin Rehabil* 2000;14:145–52.
38 Ramanujam A, Momeni K, Ravi M, *et al*. Dynamic Margins of Stability During Robot-Assisted Walking in Able-Bodied Individuals: A Preliminary Study. *Front Robot AI* 2020;7:574365.
39 Militskova A, Mukhametova E, Fatykhova E, *et al*. Supraspinal and Afferent Signaling Facilitate Spinal Sensorimotor Network Excitability After Discomplete Spinal Cord Injury: A Case Report. *Front Neurosci* 2020;14:552.
40 Krenn M, Toth A, Danner SM, *et al*. Selectivity of transcutaneous stimulation of lumbar posterior roots at different spinal levels in humans. *Biomed Tech (Berl)* 2013;58 Suppl 1.
41 Sayenko DG, Rath M, Ferguson AR, *et al*. Self-Assisted Standing Enabled by Non-Invasive Spinal Stimulation after Spinal Cord Injury. *J Neurotrauma* 2019;36:1435–50.
42 Estes S, Zarkou A, Hope JM, *et al*. Combined Transcutaneous Spinal Stimulation and Locomotor Training to Improve Walking Function and Reduce Spasticity in Subacute Spinal Cord Injury: A Randomized Study of Clinical Feasibility and Efficacy. *J Clin Med* 2021;10:1167.
43 Buehner JJ, Forrest GF, Schmidt-Read M, *et al*. Relationship between ASIA examination and functional outcomes in the NeuroRecovery Network Locomotor Training Program. *Arch Phys Med Rehabil* 2012;93:1530–40.
44 Forrest GF, Sisto SA, Barbeau H, *et al*. Neuromotor and musculoskeletal responses to locomotor training for an individual with chronic motor complete AIS-B spinal cord injury. *J Spinal Cord Med* 2008;31:509–21.
45 Cirnigliaro CM, La Fountaine MF, Parrott JS, *et al*. Administration of Denosumab Preserves Bone Mineral Density at the Knee in Persons With Subacute Spinal Cord Injury: Findings From a Randomized Clinical Trial. *JBMR Plus* 2020;4:e10375.
46 Cirnigliaro CM, La Fountaine MF, Parrott JS, *et al*. Loss of lower extremity bone mineral density 1 year after denosumab is discontinued in persons with subacute spinal cord injury. *Osteoporos Int* 2023;34:741–8.
47 Peppler WT, Kim WJ, Ethans K, *et al*. Precision of dual-energy X-ray absorptiometry of the knee and heel: methodology and implications for research to reduce bone mineral loss after spinal cord injury. *Spinal Cord* 2017;55:483–8.

48 Baim S, Wilson CR, Lewiecki EM, *et al*. Precision assessment and radiation safety for dual-energy X-ray absorptiometry: position paper of the International Society for Clinical Densitometry. *J Clin Densitom* 2005;8:371–8.
49 Pop LC, Sukumar D, Schneider SH, *et al*. Three doses of vitamin D, bone mineral density, and geometry in older women during modest weight control in a 1-year randomized controlled trial. *Osteoporos Int* 2017;28:377–88.
50 Pop LC, Sukumar D, Tomaino K, *et al*. Moderate weight loss in obese and overweight men preserves bone quality. *Am J Clin Nutr* 2015;101:659–67.
51 Medicine PVoACfSC. *Bone health and osteoporosis management in individuals with spinal cord injury*. Washington, DC, 2021.
52 Taddei F, Schileo E, Helgason B, *et al*. The material mapping strategy influences the accuracy of CT-based finite element models of bones: an evaluation against experimental measurements. *Med Eng Phys* 2007;29:973–9.
53 Rho JY, Hobatho MC, Ashman RB. Relations of mechanical properties to density and CT numbers in human bone. *Med Eng Phys* 1995;17:347–55.
54 Faul F, Erdfelder E, Lang A-G, *et al*. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behav Res Methods* 2007;39:175–91.
55 Chen S-C, Lai C-H, Chan WP, *et al*. Increases in bone mineral density after functional electrical stimulation cycling exercises in spinal cord injured patients. *Disabil Rehabil* 2005;27:1337–41.
56 Mohr T, Podenphant J, Biering-Sorensen F, *et al*. Increased bone mineral density after prolonged electrically induced cycle training of paralyzed limbs in spinal cord injured man. *Calcif Tissue Int* 1997;61:22–5.