ORIGINAL ARTICLE
An evaluation of the muscle-bone unit theory among individuals with chronic spinal cord injury

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Study design: Cross-sectional observation.

Objectives: To explore the association between muscle size and function, and indices of bone strength among a sample of adults with chronic spinal cord injury (SCI).

Setting: Ontario, Canada.

Methods: Sixty-five participants ($n=47$ men) with chronic SCI (C1-T12 American Spinal Injury Association Impairment Scale (AIS) A–D) were recruited, mean ± s.d. age 49.4 ± 12.8 years and years post-injury 14.3 ± 10.7. Muscle cross-sectional area (CSA) and indices of bone strength at the distal tibia and tibia shaft were measured by peripheral quantitative computed tomography. Muscle CSA was multiplied by tibia length to obtain muscle-bending moment (MBM), a surrogate of torque. Plantar flexor components of the lower-extremity motor scores (pf-LEMS) were used as clinical measures of muscle function. Pearson's correlations (r) were used to determine the strength of relationships.

Results: Correlations were found between MBM and indices of bone strength at the distal tibia and tibia shaft ($r=0.44–0.56$), as well as between pf-LEMS and indices of bone strength at the distal tibia and tibia shaft ($r=0.37–0.71$). pf-LEMS had a stronger association with bone variables at the distal tibia compared with MBM ($r=0.6$ vs $r=0.4$). All relationships between muscle and bone remained significant when controlling for the duration of injury.

Conclusion: It appears that lower limb muscle size and function are more strongly correlated with bone strength indices at the distal tibia than at the tibia shaft among individuals with SCI. The relationships between muscle and bone are clinically important, as muscle CSA and strength (motor scores) are potentially amenable to rehabilitation intervention(s).

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INTRODUCTION

Fragility fractures develop in 25–46% of people living with chronic spinal cord injury (SCI) and sublesional osteoporosis.[1] There is a rapid decline in bone mineral density (BMD) of the periarticular hip and knee regions within 12–18 months post motor complete SCI (AIS A–D) of 3–4% per month,[2] thereby placing individuals with chronic SCI at a high risk for developing lower-extremity fragility fractures during low-trauma events (that is, during a transfer or rolling over in bed). Fragility fractures after SCI can lead to increased morbidity, decreased functional mobility, and increased attendant care and healthcare costs.[3] A 45–80% reduction in muscle cross-sectional area (CSA) in the lower extremities has been reported acutely after motor complete SCI,[4] as well as changes in fat mass and adipose tissue deposition.[5] Therefore, bone strength is compromised after SCI as a result of rapid bone loss in parallel with a reduction in both the quantity and quality of muscle. The majority of literature describing regional changes in lower-extremity bone and muscle mass is derived from men with motor complete paraplegia with a few exceptions.

Systematic reviews of rehabilitation therapies for treatment and/or prevention of sublesional osteoporosis reveal contradictory results.[3,6]

The premise of these therapies is to apply mechanical loading and/or increase muscle function through exercise with the intent of eliciting increase in bone strength. Whether the presence of muscle function or spasticity helps to preserve lower-extremity bone mass has been proposed and debated;[6] it is unclear whether the adverse changes in bone after SCI are to some degree linked to the muscle atrophy that occurs.[7,8] Understanding the mechanisms underlying bone loss associated with neurological impairment will facilitate the development of effective strategies for preventing or treating sublesional osteoporosis and reducing lower-extremity fragility fractures after SCI.

Frost's mechanostat theory states that bone strength adapts to meet mechanical needs.[9] Muscle contractions provide the largest physiological loads on bone, and therefore a linear relationship has been proposed between muscle CSA and bone mineral content (BMC).[10] Using peripheral quantitative computed tomography (pQCT), positive associations have been demonstrated between muscle and bone geometry/density in able-bodied adults[11] and children with disability.[10,12] Further, maintaining muscle mass and strength may be an important component of fracture prevention in able-bodied persons.[13]

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Whether the muscle-bone unit theory holds true in individuals with neurological impairment has rarely been studied. Two studies reported a positive association between lean tissue mass and BMC in the legs among individuals with incomplete SCI.[7,8] However, these studies measured areal BMC using dual-energy X-ray absorptiometry, which cannot fully differentiate between bone density and bone size. Newer technologies such as pQCT can be used for a better determination of the relationships between muscle and bone geometry/density. A relationship has been shown between bone-strength-derived geometry parameters assessed with pQCT and bone fractures in chronic SCI.[14,15] A measure of the distribution of bone material around a given axis from a pQCT scan, such as cross-sectional moment of inertia or polar area moment of inertia, can indicate the bone's resistance to an imposed bending load or imposed torsion; therefore, these measures are important parameters of bone strength.[14] Section modulus is derived from the polar area moment of inertia and the maximum distance between the center of the identified area and its outer boundary; section modulus has been associated with non-vertebral fractures in older men.[15] Further, pQCT provides a measure of muscle CSA, which is reported to be an acceptable surrogate of muscle strength for the purpose of exploring associations between muscle and bone,[10,16] and is a beneficial measure among individuals with SCI due to neuromuscular deficits. A surrogate of torque exerted by a muscle can be determined from the product of muscle CSA and bone length (muscle-bending moment, MBM), and may be important to consider since bones are loaded by compression as well as bending.[11]

A study of the relationship between muscle size/function and bone geometry/density in patients with SCI will clarify whether a muscle–bone relationship is maintained in the scenario of concurrent muscle atrophy and neurological impairment. It may also provide insight into future treatment paradigms for individuals with similar neurological impairments. The current study investigates whether a relationship exists between MBM and muscle function vs indices of bone strength at the tibia using pQCT technology among a sample of adults with chronic SCI.

MATERIALS AND METHODS

Participants

Eligible participants were adults aged 20–80 years who had a SCI of traumatic etiology, C2-T12 AIS A–D of ≥2 year's duration. Participants with severe lower-extremity spasticity, a calf circumference >40 cm (diameter of >13 cm), lower-extremity metal implants, bilateral heterotopic ossification of the knee region, or combined hip and knee flexion contracture >30° were excluded. The project was approved by the local research ethics board.

Outcome assessments

Plantar flexor lower extremity motor scores (pf-LEMS) were taken from each participant's most recent International Standards for Neurologic Classification of SCI (ISNCSCI) exam, and were used to represent the functional muscle strength of the distal lower extremity.

Muscle CSA and all bone outcome data were acquired using a Stratec XCT 2000 scanner (Stratec Medizintechnik, Pforzheim, Germany). Slices sized 2.5 mm each were obtained at the distal tibia (4% tibia length; trabecular site) and tibia shaft (66% tibia length; cortical site).[17] Sixty-six percent of the tibia length was chosen because in this region the muscle CSA is the greatest.[11] The 66% site was also chosen to represent primarily cortical bone, and the 4% site was chosen to represent trabecular bone. Scans were not acquired at prior fracture sites.

The manufacturer's software (XCT version 5.50, Stratec Medizintechnik) was used for muscle CSA analysis of the images acquired at the tibia shaft. To estimate torque, muscle CSA (in cm^2) was multiplied by tibia length (in m) to obtain the MBM (in $cm^2 m$).[11] MBM is a comparable metric across

participants, and provides a more relevant measure of force-generating potential than CSA.[11]

Stratec v5.50 software was also used to analyze all bone outcomes. Cortical thickness (mm), cortical bone CSA (mm^2), total BMC ($mg\,mm^{-1}$) and section modulus (mm^3) were analyzed at the tibia shaft. Cortical thickness, cortical bone CSA and section modulus parameters were selected to represent the integrity and strength of cortical bone. Total BMC was chosen as an outcome because it has been used in previous studies exploring the muscle-bone unit theory.[10,12] Total BMC ($mg\,mm^{-1}$) and trabecular volumetric bone mineral density (vBMD) ($mg\,cm^{-3}$) were obtained at the distal tibia. The largest reported loss of bone following SCI is from the trabecular compartment; therefore, trabecular vBMD was selected as an index of bone strength. Total BMC was selected as a measure of bone size. In addition, both trabecular vBMD and total BMC outcomes at the distal tibia were chosen as they have been used in a previous study looking at the muscle-bone unit theory.[10]

Data analysis

Demographic and impairment characteristics of the participants were reported as mean (standard deviation [s.d.]) or count (%). Mean (s.d.) values were determined for all muscle and bone characteristics for the entire cohort, as well as for individuals with complete and incomplete injuries separately. Owing to the small sample size and unequal ratio of men ($n=47$) to women ($n=18$), data from both genders were pooled for analyses. pf-LEMS were correlated with calf MBM using Pearson's Correlation (r) to determine whether MBM was a good surrogate of muscle strength in SCI. pf-LEMS from the scanned leg using pQCT (right vs left) was used for all correlations. Participants with AIS A–B were assigned 0 for pf-LEMS. Six participants had missing pf-LEMS (5 AIS C, 1 AIS D); these data points were removed from analyses.

Pearson's Correlations (r) were used to investigate the associations between both MBM and pf-LEMS vs indices of bone strength. Partial correlations were conducted to determine the contribution of each muscle outcome to bone strength. Duration of injury (DOI) is an important covariate to consider as muscle atrophy occurs primarily in the first 4–6 weeks post-injury, and bone loss continues up to 2 years post-injury. Therefore, all associations were assessed while controlling for DOI. Further, to determine whether injury severity was driving the strength of the correlation, we explored whether the correlations between muscle and bone were different in magnitude between the most neurologically impaired individuals (AIS A–B) and those with incomplete injuries (AIS C–D). Statistical analyses were conducted with SPSS Predictive Analysis Software (PASW v18).

RESULTS

The sample was comprised of 65 participants who were predominantly middle-aged (49.4 ± 12.8 years) men ($n=47$) with long standing SCI (14.3 ± 10.7 years) (Table 1). Significant differences were found for all muscle and bone outcome measures between individuals with motor complete and incomplete injuries (Table 2).

A significant correlation was observed between MBM and pf-LEMS ($r=0.50$; $P<0.001$). Significant correlations between both MBM and pf-LEMS vs bone indices are shown in Table 3 and Figures 1–4. All of the relationships between MBM and bone outcomes remained significant when a partial correlation was conducted with the effect of pf-LEMS being removed (Table 3). When the effect of MBM was removed, only the relationships between pf-LEMS and bone indices at the distal tibia remained significant (Table 3). When a partial correlation was performed between MBM or pf-LEMS and bone strength controlling for DOI, all of the relationships remained significant (Table 3).

Associations between MBM and all indices of bone strength were significant among individuals with complete injuries, and they remained significant when controlling for DOI. Among individuals with incomplete injuries, however, associations were only present between MBM and indices of cortical bone strength, and between pf-LEMS and indices of trabecular bone strength. When covariates of

DOI, pf-LEMS or MBM were taken into account, these relationships remained significant (Table 3).

DISCUSSION

Sublesional osteoporosis and fracture risk are concerns in the SCI population as individuals live longer with low bone mass. The current study assessed the relationships between calf muscle size/strength and several lower-extremity bone parameters. Our results illuminate two unique findings: (1) both muscle outcomes of MBM and pf-LEMS were most strongly associated with vBMD and BMC at the distal tibia, with pf-LEMS showing the most robust correlations at this site; and (2) the relationship between muscle and bone was strongest among the individuals with motor complete injuries.

Significant relationships were found between muscle and bone among individuals with SCI, although in most cases the strength of the relationship was moderate ($r=0.37$–0.71). Our results indicate that the muscle–bone relationship exists after SCI, but is not as strong as previously reported among able-bodied persons.[10–12] The variability in muscle strength and function among a group of individuals with diverse neurological impairments may have reduced the strength of the observed muscle–bone relationship. In addition, our results demonstrate that the correlation between muscle and bone measures persists after controlling for DOI, suggesting that injury duration is not driving the relationship.

Both lower-limb MBM and pf-LEMS were most strongly associated with trabecular vBMD and total BMC at the distal tibia.[18] Consistent with our findings, when muscular activity of the plantar flexors was reintroduced in a study of seven people with motor complete SCI by an electrical simulation training program, there was an increase in trabecular BMD at the distal tibia.[19] In addition, a strong linear relationship has been reported between muscle CSA and BMC at the distal tibia site in children.[10] Although the associations were strongest between muscle and trabecular bone, we also found relationships between muscle and cortical bone. A heterogeneous reduction in cortical wall thickness is characteristic of bone loss after SCI,[20,21] and the tibia shaft is a site of plantar flexor origin of muscle attachment and therefore a site of direct pulling of muscle on bone. It has been suggested that heterogeneous thinning of the cortical shaft is related to fractures in SCI.[21] A previous study reported a strong significant linear relationship between calf muscle density and cortical bone density in the tibia among individuals who have suffered stroke,[22] and another study demonstrated modest exercise-induced changes in the cortical bone strength of the radius that were correlated with increases in muscle size among adolescent female tennis players.[23] Our results indicate that there are relationships between muscle and both trabecular and cortical bone in the lower extremity after chronic SCI, the stronger relationship existing with trabecular bone.

Maintaining residual muscle strength in individuals with SCI may be important for preservation of trabecular bone strength. pf-LEMS was chosen to represent the actual muscle-force-generating ability in the present study. A unique finding was that pf-LEMS was more highly correlated with the measured indices of bone strength at the distal tibia than MBM. Previous work has suggested that among the able-bodied men and women, muscle strength or grip strength was a stronger determinant of distal radius bone mechanical characteristics when compared with muscle CSA.[24] Consistent with previous work, our data suggest that preservation of muscle strength, and not just size, may be important for maintaining trabecular bone strength, potentially attenuating fracture risk.

It must be noted, however, that although the use of LEMS is a feasible and an appealing means of quantifying muscle-force-generating ability in the present population, it is ultimately a subjective muscle strength outcome. In a clinical sense, the ISNCSCI has good-to-excellent inter-rater reliability; however, the true validity of the measure in the present context is unknown. pf-LEMS was correlated with MBM and muscle CSA in our study, and correlations between muscle CSA and strength have been reported in previous studies.[16,22] We demonstrated that MBM was a stronger correlate of bone measures than muscle CSA (data not shown), and others

Table 1 Demographic and impairment characteristics

N	65
Ratio men:women	3:1 (47 men, 18 women)
Age (years)[a]	49.37 ± 12.80
Height (cm)[a]	175.62 ± 8.25
Weight (kg)[a]	80.31 ± 20.69
DOI (years)[a]	14.27 ± 10.72
Paraplegic AIS A–B	19
Paraplegic AIS C–D	12
Tetraplegic AIS A–B	14
Tetraplegic AIS C–D	20
Average pf-LEMS AIS C–D	2

Abbreviations: AIS, American Spinal Injury Association Impairment Scale; DOI, duration of injury; N, sample size; pf-LEMS, plantar flexor lower extremity motor scores.
[a]Reported as average ± s.d.

Table 2 Muscle and bone characteristics

Outcome (n=65)	Average ± s.d.		
	Total	AIS A–B (n=33)	AIS C–D (n=32)
Muscle CSA (mm^2)	4586.08 ± 1966.29	3386.32 ± 1284.79	$5823.34 \pm 1779.22^*$
MBM (cm^2 m)	17.99 ± 8.03	13.07 ± 5.21	$23.07 \pm 7.24^*$
Cortical bone CSA 66% (mm^2)	273.89 ± 80.29	244.20 ± 75.98	$304.51 \pm 73.78^*$
Cortical thickness 66% (mm)	3.40 ± 0.97	3.07 ± 1.01	$3.73 \pm 0.80^*$
Total BMC 66% (mg mm^{-1})	372.50 ± 89.90	340.57 ± 81.94	$405.42 \pm 86.89^*$
SM 66% (mm^3)	2545.75 ± 901.03	2265.37 ± 750.20	$2834.9 \pm 961.84^*$
Trabecular vBMD 4% (mg cm^{-3})	138.70 ± 55.91	100.58 ± 37.01	$176.82 \pm 44.53^*$
Total BMC 4% (mg mm^{-1})	225.89 ± 94.85	168.20 ± 54.98	$283.57 \pm 91.59^*$

Abbreviations: BMC, bone mineral content; CSA, cross-sectional area; MBM, muscle-bending moment; SM, section modulus; vBMD, volumetric bone mineral density.
*$P<0.005$ controlling for motor completeness of injury.

Table 3 Correlations between indices of muscle and indices of bone

	MBM (cm² m)	MBM (effect pf-LEMS removed)	MBM (controlling for DOI)	pf-LEMS	pf-LEMS (effect MBM removed)	pf-LEMS (controlling for DOI)
Cortical bone CSA 66% (mm²)	r=0.54; P<0.001	r=0.45; P<0.001	r=0.49; P<0.001	r=0.40; P=0.001	r=0.17; P=0.210	r=0.32; P=0.015
Cortical thickness 66% (mm)	r=0.44; P<0.001	r=0.37; P=0.004	r=0.38; P=0.002	r=0.37; P=0.004	r=0.16; P=0.230	r=0.28; P=0.037
Total BMC 66% (mg mm⁻¹)	r=0.54; P<0.001	r=0.45; P<0.001	r=0.49; P<0.001	r=0.40; P=0.002	r=0.17; P=0.217	r=0.32; P=0.016
SM 66% (mm³)	r=0.53; P<0.001	r=0.44; P<0.001	r=0.49; P<0.001	r=0.37; P=0.004	r=0.13; P=0.314	r=0.30; P=0.021
Trabecular vBMD 4% (mg cm⁻³)	r=0.55; P<0.001	r=0.42; P=0.001	r=0.52; P<0.001	r=0.68; P<0.001	r=0.56; P<0.001	r=0.64; P<0.001
Total BMC 4% (mg mm⁻¹)	r=0.56; P<0.001	r=0.40; P=0.002	r=0.53; P<0.001	r=0.71; P<0.001	r=0.60; P<0.001	r=0.67; P<0.001
AIS A–B						
Cortical bone CSA 66% (mm²)	r=0.43; P=0.013	—	r=0.42; P=0.020	—	—	—
Cortical Thickness 66% (mm)	r=0.40; P=0.022	—	r=0.38; P=0.035	—	—	—
Total BMC 66% (mg mm⁻¹)	r=0.44; P=0.010	—	r=0.43; P=0.015	—	—	—
SM 66% (mm³)	r=0.40; P=0.020	—	r=0.39; P=0.027	—	—	—
Trabecular vBMD 4% (mg cm⁻³)	r=0.40; P=0.024	—	r=0.40; P=0.027	—	—	—
Total BMC 4% (mg mm⁻¹)	r=0.46; P=0.009	—	r=0.45; P=0.011	—	—	—
AIS C–D						
Cortical bone CSA 66% (mm²)	r=0.42; P=0.018	r=0.48; P=0.016	r=0.41; P=0.024	r=0.29; P=0.152	r=0.30; P=0.140	r=0.28; P=0.170
Cortical thickness 66% (mm)	r=0.25; P=0.161	r=0.35; P=0.087	r=0.24; P=0.203	r=0.29; P=0.146	r=0.30; P=0.151	r=0.27; P=0.188
Total BMC 66% (mg mm⁻¹)	r=0.43; P=0.014	r=0.49; P=0.013	r=0.42; P=0.019	r=0.30; P=0.137	r=0.32; P=0.122	r=0.30; P=0.138
SM 66% (mm³)	r=0.46; P=0.008	r=0.50; P=0.012	r=0.46; P=0.010	r=0.26; P=0.209	r=0.27; P=0.196	r=0.27; P=0.196
Trabecular vBMD 4% (mg cm⁻³)	r=0.11; P=0.558	r=-0.09; P=0.970	r=0.06; P=0.734	r=0.48; P=0.012	r=0.48; P=0.014	r=0.40; P=0.048
Total BMC 4% (mg mm⁻¹)	r=0.22; P=0.229	r=0.18; P=0.400	r=0.19; P=0.301	r=0.56; P=0.003	r=0.57; P=0.003	r=0.51; P=0.009

Abbreviations: AIS, American Spinal Injury Association Impairment Scale; BMC, bone mineral content; CSA, cross-sectional area; DOI, duration of injury; MBM, muscle-bending moment; pf-LEMS, plantar flexor lower extremity motor score; SM, section modulus; vBMD, volumetric bone mineral density.
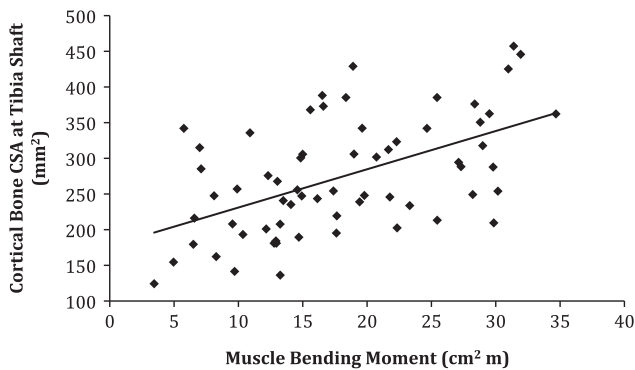

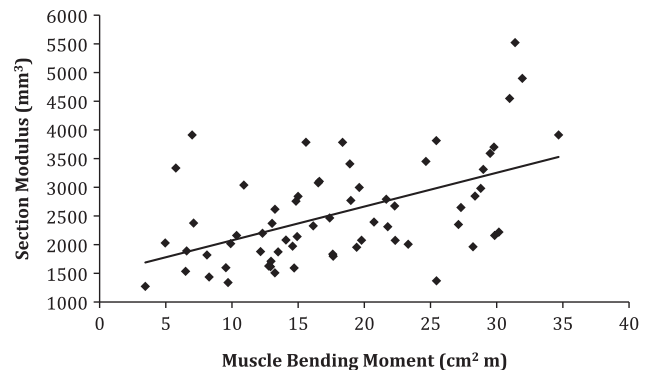**Figure 1** Cortical bone CSA at tibia shaft (mm²) vs MBM (cm² m); r=0.54; P<0.001.

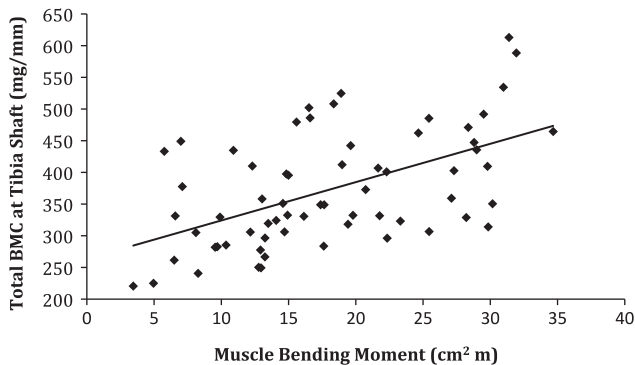**Figure 3** Section modulus at tibia shaft (mm³) vs MBM (cm² m); r=0.53; P<0.001.

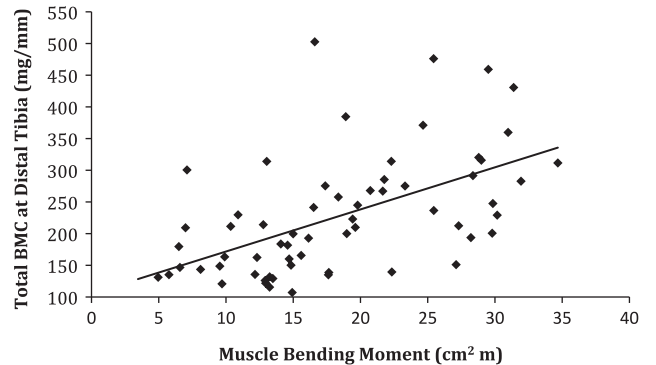**Figure 2** Total BMC at tibia shaft (mg mm⁻¹) vs MBM (cm² m); r=0.54; P<0.001.

Figure 4 Total BMC at distal tibia (mg mm⁻¹) vs MBM (cm² m); r=0.56; P<0.001.

have estimated muscle torque in relation to bone density and geometry and found relationships of similar or stronger magnitude to the present study data.[11] These findings suggest that estimates of muscle torque may be preferable as correlates of bone strength in future studies.

Another unique finding of the study is that when we evaluated the muscle–bone relationship separately in individuals with motor complete and incomplete injuries, all the correlations remained significant within the motor complete SCI group, but only between MBM and cortical bone, and pf-LEMS and trabecular bone within the incomplete SCI group. A previous study supports our findings; they reported significant associations between leg lean mass and BMD and BMC in people with motor complete SCI.[25] Further, a recent study showed a significant relationship between muscle density and cortical bone density among individuals who had recently suffered a stroke, paralleling incomplete neurological loss.[22] The small sample size, missing muscle strength data (pf-LEMS), and varying influence of the autonomic nervous system likely contribute to the discrepancy in muscle–bone relationships between the complete and incomplete groups in the present study. The incomplete group demonstrated larger variability in total BMC at the distal tibia, which may also contribute to the difference in the strength of the muscle–bone relationship.

Several limitations should be acknowledged: the lack of adjustment for potential confounders, small sample size ($n=65$), and diversity of participants' age and injury level. The diversity of neurological impairments among members of our cohort may be viewed as the strength of our study because it allowed for a broader range of muscle areas. Larger samples are needed to determine if the observed relationships between muscle strength or size and bone strength persist after controlling for important correlates such as age, gender or completeness of injury. Further, it would have been ideal to measure distal femur and proximal tibia bone outcomes as they are the most common sites of bone loss and fracture; we were unable to measure the outcomes of interest at these sites with the available pQCT technology. However, bone loss at the distal tibia has been associated with prevalent fractures after SCI.[26]

In summary, significant correlations were found between muscle strength and bone geometry/density in the lower limb of individuals with chronic SCI. The relationship was strongest at the distal tibia, and was not influenced by DOI. When the present cohort was separated by severity of injury, correlations were stronger among individuals with complete SCI. The relationships between muscle and bone are clinically important, as muscle strength and muscle CSA are potentially amenable to current rehabilitation interventions. In addition, maintenance of muscle strength may be an important contributor to the prevention of fracture. Future research in this area should explore the contributions of muscle strength or size to fracture-risk reduction among patients with SCI and sublesional osteoporosis.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

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