Ambulatory function in motor incomplete spinal cord injury: a magnetic resonance imaging study of spinal cord edema and lower extremity muscle morphometry

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Study design: This research utilized a cross-sectional design.

Objectives: Spinal cord edema length has been measured with T2-weighted sagittal MRI to predict motor recovery following spinal cord injury. The purpose of our study was to establish the correlational value of axial spinal cord edema using T2-weighted MRI. We hypothesized a direct relationship between the size of damage on axial MRI and walking ability, motor function and distal muscle changes seen in motor incomplete spinal cord injury (iSCI).

Setting: University-based laboratory in Chicago, IL, USA.

Methods: Fourteen participants with iSCI took part in the study. Spinal cord axial damage ratios were assessed using axial T2-weighted MRI. Walking ability was investigated using the 6-min walk test and daily stride counts. Maximum plantarflexion torque was quantified using isometric dynometry. Muscle fat infiltration (MFI) and relative muscle cross-sectional area (rmCSA) were quantified using fat/water separation magnetic resonance imaging.

Results: Damage ratios were negatively correlated with distance walked in 6 min, average daily strides and maximum plantarflexion torque, and a negative linear trend was found between damage ratios and lower leg rmCSA. While damage ratios were not significantly correlated with MFI, we found significantly higher MFI in the wheelchair user participant group compared to community walkers.

Conclusions: Damage ratios may be useful in prognosis of motor recovery in spinal cord injury. The results warrant a large multi-site research study to investigate the value of high-resolution axial T2-weighted imaging to predict walking recovery following motor incomplete spinal cord injury.

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INTRODUCTION

Annually, an estimated 250 000–500 000 individuals suffer a spinal cord injury (SCI) worldwide.1 Incomplete spinal cord injury refers to a type of SCI where partial sensory and/or motor function is, to some degree, preserved below the level of the injury.2 Generally, patients with motor incomplete spinal cord injury (iSCI) are expected to recover at least some walking ability3 but not without deficits in generating maximal volitional torque.4 The size and volitional activation of the lower extremity musculature is likely to factor4,5 in maximizing ambulatory recovery, which remains a top priority in rehabilitative programs.6 An expected adaptation of motor incomplete spinal cord injury is change in muscle structure distal to the level of injury7,8 (for example, decreased muscle cross-sectional area (atrophy), and muscle fat infiltration (MFI)).9–11 While atrophy and MFI of lower extremity muscle can be quantified using magnetic resonance imaging (MRI),9,12 their directional relationship to the damaged area of the cervical cord and ambulatory status are largely unknown.

Predicting neurologic functional recovery in cervical spinal cord injury with postoperative MRI has been widely utilized.13–22 A number of studies have demonstrated that edema without hemorrhage in the cervical cord suggests a more favorable functional outcome with iSCI.14,15,17 Further work has measured and related the length of edema to motor abilities and prognosis.13–15,23,24 However, due to insufficient T2 contrast in the damaged cord, questions remain regarding the prognostic value of such an approach.25

With technological advancements in today’s and tomorrow’s MRI sequences, the quantification of spinal cord edema and its predictive relationship to muscle health and motor function (for example, walking ability,26 decreased lower extremity maximum torque output,4 decreased muscle cross-sectional area (atrophy) distal to the injury site,12 and muscle fat infiltration9–11) may be realized. The purpose of this cross-sectional study was to use high-resolution axial T2-weighted MRI to quantify spinal cord edema in participants with iSCI, and to relate this metric of cord damage to walking ability (6-min walk test and daily stride count), lower extremity torque production, lower extremity muscle CSA, and MFI. We hypothesized that spinal cord edema would be negatively correlated with walking ability, torque production, and muscle CSA, but positively...
correlated with the lower extremity MFI. For a secondary analysis, we hypothesized wheelchair ambulators to have higher MFI and lower muscle CSA compared to those not requiring a wheelchair.

**MATERIALS AND METHODS**

**Participant characteristics**

Participants were recruited from the Rehabilitation Institute of Chicago’s Spinal Cord Injury database, in accordance with Northwestern University IRB #STU0087983 and the Declaration of Helsinki. Fourteen individuals with chronic cervical iSCI participated (1 female and 13 males, average age = 43 ± 12 years old). Four individuals with iSCI were classified using the American Spinal Cord Injury Association Impairment Scale (AIS) as AIS C C5-8 level, 2 participants were classified as AIS D C1-4 level, and 8 participants were classified as AIS D C5-8 level. Seven participants used walking as their primary mode of community ambulation, while seven used wheelchairs for community ambulation. See Table 1 for details on the participant characteristics, including time since injury.

We certify that all applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during the course of this research.

**MAGNETIC RESONANCE IMAGING**

**Spinal cord imaging**

T2-weighted imaging of the cervical spinal cord was performed using a 3.0 Tesla Prisma magnetic resonance (MR) scanner equipped with a 64-channel head/neck coil (Siemens, Erlangen, Germany). A high-resolution T2-weighted structural image of the cervical spine and spinal cord damage site was acquired using a 2D turbo spin echo sequence, and 16 slices were oriented to be perpendicular to the spinal cord edema. For each participant, using the slice where the spinal cord edema of maximum area was measured, the cross-sectional area of edema was obtained, and a damage ratio was calculated as maximum spinal cord edema CSA divided by the CSA of the surrounding spinal cord. A value of zero suggests no edema, where a value of one equates to the edema covering the full region of the spinal cord (Figure 1).

**6-min walk test**

Each participant completed an over ground 6-min walk test, where the total distance walked within a 6-min time frame was measured. Participants were instructed to walk at their normal, self-selected pace, and were allowed to use assistive devices and braces as necessary. The 6-min walk test has been shown to be reliable and valid in iSCI.

**Daily stepping**

Each participant wore an ankle step monitor with an accelerometer for a 2-week window, in order to quantify average daily strides. Participants were instructed to wear the step monitor at all times except when bathing/showering. Previous literature verified that a ≥3-day window of acquiring step data is sufficient for a reliable estimate of stepping activity.

**Walking index for spinal cord injury**

A licensed physical therapist rated each participant on a locomotor scale, the Walking Index for Spinal Cord Injury II. This scale ranks the ability of the participant to walk 10 meters, and has been demonstrated to have excellent inter-rater reliability and to be a valid tool in SCI.

**Isometric plantarflexion torque**

For isometric ankle plantarflexion torque measurement, participants were secured in a seated position with both ankles at neutral, knees flexed at 20°, and hips flexed to 75°. Maximum volitional torque (MVT) was established following three maximal isometric contractions of the plantarflexors, each contraction held 3–4 s duration in an isokinetic dynamometer, with each leg tested separately (Biodex Rehabilitation System v3, Shirley, NY, USA). Verbal encouragement to facilitate maximum torque production was provided. Torque traces were monitored during each trial on a biofeedback screen.

**Muscle fat infiltration and lower extremity muscle CSA**

For both the leg muscle cross-sectional area and muscle fat infiltration quantification, a chemical shift based, 3D dual-echo gradient, Dixon method fat-water separation MRI technique was performed on all participants. The 2-point Dixon examination included the major muscle groups of the lower leg: gastrocnemius, soleus, tibialis
Sixty slices were obtained through the leg, and averages were taken across 10 consecutive slices of muscle bulk, total CSA values were taken as a sum of all 4 muscles, and the relative muscle CSA (rmCSA) was calculated by removing the fat infiltration, using the equation:

\[ \text{rmCSA} = \text{CSA} \times (1 - \text{MFI}). \]

**Statistical analyses**

All statistical analyses of the data were performed using IBM SPSS (Version 21, Armonk, NY, USA). All data were tested for normality using Kolmogorov–Smirnov statistical analyses. Intra-class correlation coefficients (ICC 2, 1) were used to test the inter- and intra-rater reliability of the spinal cord damage ratio measure. Rater one took measurements two months apart for intra-rater testing, and rater two took a separate measure of damage ratios to establish inter-rater reliability. Pearson correlations were employed to examine linear relationships between spinal cord damage ratios and distance walked in 6 min, average daily strides, plantarflexion torque production, relative muscle CSA, and MFI. A 2-way ANOVA was utilized to test for significant MFI differences between wheelchair user and community walker participant groups, as well as between the four muscle groups, with Bonferroni post hoc correction. An independent samples t-test was used to test for a significant difference in total lower leg total CSA between the wheelchair user and community walker participant groups. *P*-values of <0.05 were considered significant.

**RESULTS**

All of the data met assumptions of normality using Kolmogorov–Smirnov statistical analyses. Individual data are presented in Tables 2 and 3.

**Spinal cord imaging**

The damage ratio measurement showed high inter-rater (ICC 2, 1 = 0.82) and high intra-rater reliability (ICC 2, 1 = 0.92). Damage ratios were negatively correlated with distance walked in 6 min (*R* = −0.72, *P* < 0.01, Figure 2a), average daily strides (*R* = −0.74, *P* < 0.01, Figure 2b), and isometric plantarflexion MVT (*R* = −0.61, *P* = 0.02, Figure 2c). Damage ratios were also negatively correlated with the Walking Index for Spinal Cord Injury II scores (Spearman’s rho = −0.70, *P* < 0.01). A non-significant negative linear trend was found between damage ratios and lower leg total CSA (*R* = −0.50, *P* = 0.06). Damage ratios were not significantly correlated with MFI (*R* = 0.30, *P* = 0.31).

**Isometric plantarflexion torque**

Isometric plantarflexion MVT was significantly positively correlated with plantarflexor rmCSA (*R* = 0.53, *P* < 0.01). This relationship held when the weaker sided MVT was correlated with the weaker plantarflexor rmCSA (*R* = 0.55, *P* = 0.04) and when the stronger sided...
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The wheelchair user participant group had significantly elevated lower extremity MFI compared to the community walker group (F = 17.62, df = 1, P < 0.01, mean difference = 6.38, Figure 3c). The peroneus longus had higher MFI compared to the tibialis anterior (F = 3.91, df = 3, mean difference = 6.93, P = 0.01), otherwise there were no significant differences between the other muscle groups. There were no significant interaction effects. There were no significant differences in leg rmCSA between groups (mean difference = 958 mm², P = 0.28).

DISCUSSION
This study demonstrated a negative correlation between damaged cord ratios and both walking ability and plantarflexion torque output in participants with iSCI. These findings suggest that axial spinal cord damage ratios on high-resolution T2-weighted MRI may be useful in predicting recovery of walking ability early after spinal cord injury. However, important questions must be addressed. How soon following injury can the extent of the spinal cord edema be used in such a predictive model? Evidence from canine and murine weight-drop contusion models of SCI found a 2-week time point for the initial formation of a fluid-filled cavity and a 4-week time point for completed edema formation.66 Human work into SCI found that spinal cord edema was visualized using sagittal T2-weighted MRI within approximately 3–4 days post injury.17

Previous literature evinced the length of the spinal cord edema on T2-weighted MRI was related to neurological status tested using ASIA and Frankel classifications.13,37,38 One study showed that edema length was negatively linearly correlated with the Functional Independence Measure (FIM) locomotor score (R = −0.22) and with the FIM motor scale (R = −0.36) upon discharge.23 Using advanced but available spinal cord fiber tractography (FT), a positive correlation was reported between FT parameters and upper extremity motor scores post SCI (Spearman’s rho range = 0.648–0.794).39 For a secondary analysis of our data, focusing on our clinical measures, we found that damage ratios were significantly negatively correlated with FIM locomotor scores (Spearman’s rho = −0.62, P = 0.02), ASIA lower extremity motor scores (Spearman’s rho = −0.72, P < 0.01), and the Walking motor scores (Spearman’s rho range = 0.624–0.778, P = 0.02).39

Table 2 Individual participant data—damage ratios, walking and plantarflexion torque

| Participant # | Primary ambulation | Damage ratio | 6MW distance (m) | Average daily strides | Right plantarflexion MVT (Nm) | Left plantarflexion MVT (Nm) |
|---------------|--------------------|--------------|-----------------|-----------------------|------------------------------|------------------------------|
| iSCI1         | Wheelchair         | 0.29         | 64              | 247                   | 30.03                        | 45.52                        |
| iSCI2         | Walk with AD      | 0.20         | 187             | 2036                  | 64.45                        | 82.93                        |
| iSCI3         | Walk with AD      | 0.39         | 147             | 1166                  | 93.00                        | 86.00                        |
| iSCI4         | Walk with AD      | 0.35         | 134             | 1557                  | 29.56                        | 44.35                        |
| iSCI5         | Walk              | 0.32         | 409             | 1483                  | 72.98                        | 149.05                       |
| iSCI6         | Walk              | 0.10         | 412             | 2786                  | 133.29                       | 104.91                       |
| iSCI7         | Wheelchair        | 0.47         | 49              | 372                   | 12.69                        | 52.80                        |
| iSCI8         | Wheelchair        | 0.57         | 90              | 330                   | 29.73                        | 12.66                        |
| iSCI9         | Walk              | 0.17         | 431             | 3077                  | 61.26                        | 83.56                        |
| iSCI10        | Walk with AD      | 0.49         | 165             | 1108                  | 55.46                        | 68.29                        |
| iSCI11        | Wheelchair        | 0.39         | 98              | 745                   | 36.13                        | 80.84                        |
| iSCI12        | Wheelchair        | 0.32         | 244             | 879                   | 95.61                        | 92.40                        |
| iSCI13        | Wheelchair        | 0.43         | 166             | 1681                  | 57.85                        | 49.25                        |
| iSCI14        | Wheelchair        | 0.34         | 241             | 2035                  | 47.59                        | 37.70                        |

Abbreviations: MVT, maximum voluntary torque; 6MW, 6 min walk test.

Table 3 Individual participant data—leg muscle measures

| Participant # | Primary ambulation | Weaker leg MFI average % | Stronger leg MFI average % | Weaker leg rmCSA (mm²) | Stronger leg rmCSA (mm²) | Weaker plantarflexion MVT (Nm) | Stronger plantarflexion MVT (Nm) |
|---------------|--------------------|--------------------------|---------------------------|-----------------------|-------------------------|-------------------------------|-------------------------------|
| iSCI1         | Wheelchair         | 15.77                    | 20.49                     | 3419.24               | 3316.51                 | 2427.90                       | 2374.22                       |
| iSCI2         | Walk with AD      | 10.55                    | 10.18                     | 5474.11               | 5645.74                 | 3777.80                       | 4530.76                       |
| iSCI3         | Walk with AD      | 16.40                    | 18.59                     | 3638.03               | 3479.53                 | 2796.45                       | 2646.78                       |
| iSCI4         | Walk with AD      | 14.76                    | 13.50                     | 3416.86               | 3740.00                 | 2135.72                       | 2631.87                       |
| iSCI5         | Walk              | 18.17                    | 11.49                     | 4199.98               | 5798.23                 | 2766.60                       | 4377.06                       |
| iSCI6         | Walk              | 17.12                    | 15.77                     | 4967.27               | 5167.29                 | 3638.70                       | 3856.84                       |
| iSCI7         | Wheelchair        | 14.85                    | 14.56                     | 4547.62               | 5437.89                 | 3488.80                       | 4328.72                       |
| iSCI8         | Wheelchair        | 15.59                    | 15.17                     | 3493.28               | 3595.58                 | 2298.98                       | 2480.93                       |
| iSCI9         | Walk              | 8.27                     | 7.38                      | 4312.88               | 4260.17                 | 3127.48                       | 3136.14                       |
| iSCI10        | Walk with AD      | 9.44                     | 14.66                     | 4095.98               | 2848.33                 | 3035.90                       | 2217.98                       |
| iSCI11        | Wheelchair        | 15.05                    | 15.68                     | 3015.63               | 2858.92                 | 2244.92                       | 2099.31                       |
| iSCI12        | Wheelchair        | 19.57                    | 21.47                     | 4860.93               | 4437.77                 | 3673.20                       | 3266.37                       |
| iSCI13        | Wheelchair        | 41.23                    | 26.98                     | 3751.46               | 3837.91                 | 2740.81                       | 2443.50                       |
| iSCI14        | Wheelchair        | 20.08                    | 19.09                     | 4037.51               | 3725.69                 | 3077.57                       | 2692.69                       |

Abbreviations: MFI, muscle fat infiltration; rmCSA, relative muscle cross-sectional area; 6MW, 6 min walk test.

MVT was correlated with the stronger sided plantarflexion rmCSA (R = 0.54, P = 0.04).

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Index for Spinal Cord Injury II (Spearman’s rho = -0.70, P<0.01). See Table 4 for individual clinical measures.

Additionally, we observed a negative linear trend between damage ratios and leg rmCSA, and found that rmCSA was significantly correlated with ability to generate plantarflexion torque. These findings are in accordance with previous research reporting decreased lower extremity CSA and decreased torque production in iSCI.

One surprising finding was that damage ratios were not significantly correlated with lower extremity MFI. Though denervation is one established cause of increased MFI, other factors such as physical inactivity, altered metabolic function, and overall weight gain certainly play a role. One theory is that while the spinal cord injury may dictate overall motor function, the amount of muscle fat infiltration may be more related to the post-injury physical activity levels on a patient-by-patient basis. Indeed, when our participants were subgrouped into wheelchair users versus community walkers, a significant lower extremity MFI difference was found. This finding is in-line with previous research where patients with iSCI had significantly higher lower extremity MFI than able-bodied matched controls.

Future direction
Using qualitative MRI parameters (that is, presence/absence of edema) along with clinical metrics, researchers used a multiple regression model to create a clinical prediction rule for determining long-term functional outcome following spinal cord injury, reporting an $R^2$ value of 0.52. We believe that our quantitative damage ratio metric may be valuable for a clinical prediction rule of future walking ability. Damage ratios alone yielded an $R^2$ value of 0.52 when correlating with distance walked in 6 min. After selecting the three most robust variables from our data set, we created a multiple regression equation using damage ratios, ASIA lower extremity motor scores (LEMS), and average plantarflexion MVT to predict average daily strides.

Multiple Regression Equation:

$$\text{Average strides} = -1547 (\text{damage ratio})$$
$$+ 90 (\text{ASIA LEMS}) - 9 (\text{MVT}) - 858, \quad R^2 = 0.77, \quad F = 10.94, \quad P < 0.01.$$  

With an $R^2$ of 0.77, this type of multiple regression analysis using quantitative MRI parameters may be useful for predicting walking ability following spinal cord injury. While we acknowledge that these data were measured in the chronic state, we believe these strong relationships warrant longitudinal investigation.

Limitations
An inherent limitation of this cross-sectional study remains our inability to provide a cause-and-effect relationship between the

Figure 2 Damage ratios versus meters walked in 6 min (a), average daily strides (b), and isometric plantarflexion maximum voluntary torque (c). Significant negative linear correlations were found ($R = -0.72, P < 0.01; R = -0.74, P < 0.01; R = -0.61, P = 0.02$; respectively). Wheelchair user participants are identified as circular data points, while community ambulator participants are identified as triangular data points.
amount of spinal cord damage and ambulatory ability. However, once the optimal time-course for axial T2 imaging of spinal cord edema is established, the prognostic value of the cord edema ratio measure towards predicting ambulatory recovery should be further explored.

CONCLUSION
In this study, we demonstrated that measurement of spinal cord edema using high-resolution axial T2-weighted imaging is possible and that damage ratios were negatively correlated with ambulatory status as well as plantarflexion torque generation in 14 participants with iSCI. The seven community walkers had significantly lower MFI in their lower extremities compared to the seven using a wheelchair. A large multi-site investigation is warranted to examine the value of high-resolution axial T2-weighted imaging to predict walking recovery following motor incomplete spinal cord injury.

DATA ARCHIVING
There were no data to deposit.

CONFLICT OF INTEREST
Elliott JM and Parrish TB—Relevant financial activities outside the submitted work: board membership, consultancy, other (Pain ID LLC), payment for lectures. The remaining authors declare no conflict of interest.

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| Participant # | Primary ambulation | Damage ratio | FIM locomotor (out of 7) | WISCI II (out of 20) | ASIA LEMS left (out of 25) | ASIA LEMS right (out of 25) |
|---------------|-------------------|--------------|--------------------------|---------------------|--------------------------|--------------------------|
| iSCI1         | Wheelchair        | 0.29         | 5                        | 13                  | 15                       | 14                       |
| iSCI2         | Walk with AD      | 0.20         | 6                        | 16                  | 24                       | 19                       |
| iSCI3         | Walk with AD      | 0.39         | 6                        | 15                  | 19                       | 23                       |
| iSCI4         | Walk with AD      | 0.35         | 6                        | 19                  | 24                       | 14                       |
| iSCI5         | Walk              | 0.32         | 7                        | 20                  | 25                       | 20                       |
| iSCI6         | Walk              | 0.10         | 7                        | 20                  | 23                       | 25                       |
| iSCI7         | Wheelchair        | 0.47         | 2                        | 6                   | 19                       | 8                        |
| iSCI8         | Wheelchair        | 0.57         | 1                        | 6                   | 8                        | 10                       |
| iSCI9         | Walk              | 0.17         | 7                        | 20                  | 25                       | 22                       |
| iSCI10        | Walk with AD      | 0.49         | 6                        | 16                  | 16                       | 14                       |
| iSCI11        | Wheelchair        | 0.39         | 6                        | 9                   | 23                       | 10                       |
| iSCI12        | Wheelchair        | 0.32         | 6                        | 19                  | 23                       | 15                       |
| iSCI13        | Wheelchair        | 0.43         | 6                        | 13                  | 19                       | 22                       |
| iSCI14        | Wheelchair        | 0.34         | 6                        | 15                  | 17                       | 24                       |

Abbreviations: ASIA LEMS, American Spinal Cord Injury Association Lower Extremity Motor Scores; FIM, functional independence measure; WISCI, walking index for spinal cord injury.
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