

ORIGINAL ARTICLE

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 dynamometry. 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.

Spinal Cord (2017) **55**, 672–678; doi:10.1038/sc.2017.18; published online 28 February 2017

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 factor^{4,5} 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 injury^{7,8} (for example, decreased muscle cross-sectional area (atrophy), and muscle fat infiltration (MFI)).^{9–11} While atrophy and MFI of lower extremity musculature can be quantified using magnetic resonance imaging (MRI),^{5,12} 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 infiltration^{9–11}) 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

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Received 3 June 2016; revised 25 January 2017; accepted 28 January 2017; published online 28 February 2017

Table 1 Participant characteristics

Participant #	Gender	Age (years)	Height (cm)	Weight (kg)	BMI (units)	Time since injury (years)	Mechanism of injury	Level of injury	ASIA impairment Scale	Primary ambulation
iSCI1	M	53	185	82.1	23.9	6	MVC	C5	C	Wheelchair
iSCI2	M	57	178	79.4	25.1	8	Cycling Injury	C3	D	Walk with AD
iSCI3	F	52	157	83.9	33.8	0.5	MVC	C6	D	Walk with AD
iSCI4	M	31	178	72.6	23.0	4	Diving Injury	C5	D	Walk with AD
iSCI5	M	28	188	95.3	27.0	3	Diving Injury	C5	D	Walk
iSCI6	M	50	168	83.9	29.9	2	Fall from Height	C6	D	Walk
iSCI7	M	30	193	115.7	31.0	4	Diving Injury	C6	C	Wheelchair
iSCI8	M	27	191	86.2	23.7	4	Skiing Injury	C5	C	Wheelchair
iSCI9	M	32	173	81.7	27.4	5	MVC	C7	D	Walk
iSCI10	M	45	175	59.0	19.2	4	ATV Injury	C3	D	Walk with AD
iSCI11	M	36	185	73.5	21.4	2	Motorcycle Injury	C6	C	Wheelchair
iSCI12	M	50	178	72.6	23.0	5	Fall from Height	C4	D	Wheelchair
iSCI13	M	64	175	108.9	35.5	4	Fall	C5	D	Wheelchair
iSCI14	M	52	175	70.3	22.9	31	Diving injury	C5	D	Wheelchair

Abbreviations: AD, assistive device; ATV, all terrain vehicle; BMI, body mass index; MVC, motor vehicle collision.

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 #STU00087983 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 (FOV = 260 mm square field of view, TR = 2380 ms, TE = 102 ms, flip angle = 120° , number of averages = 3, bandwidth = 651 Hz/Px, phase encoding direct: right to left, resolution = $0.5 \times 0.5 \times 2.0 \text{ mm}^3$, acquisition matrix = 512×282). The acquisition time was 6:30 min. Spinal cord MRI data were analyzed offline using OsiriX image processing software (Pixmeo, Geneva, Switzerland). The OsiriX interpolation function was used for clearer visualization of 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.²⁷ 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.^{27,28}

Daily stepping

Each participant wore an ankle step monitor with an accelerometer for a 2-week window, in order to quantify average daily strides.²⁹ 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.³⁰

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.³¹

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.³² 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.^{33,34} The 2-point Dixon examination included the major muscle groups of the lower leg: gastrocnemius, soleus, tibialis

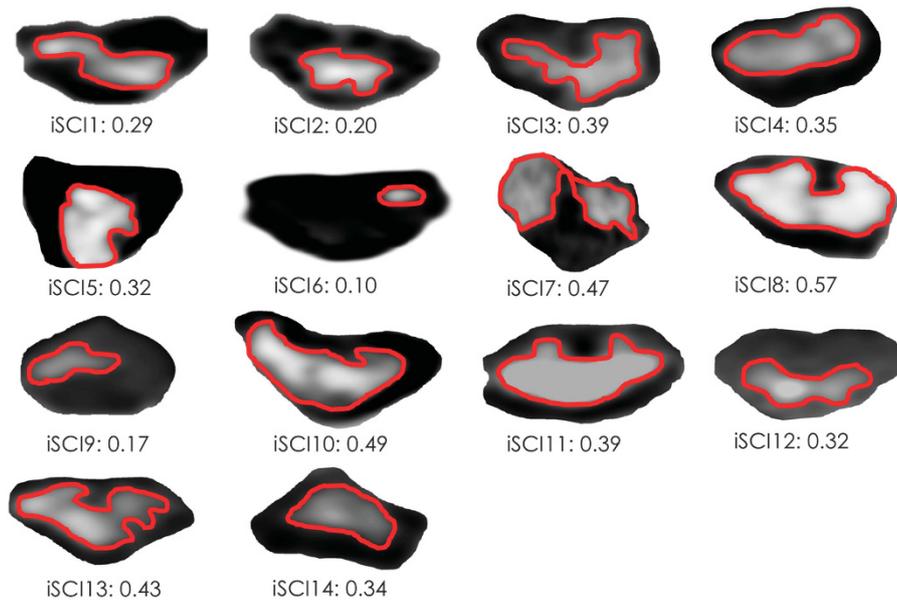


Figure 1 Axial T2-weighted images of spinal cord edema in each participant with iSCI, with corresponding damage ratios listed. Damage ratios were calculated as edema area divided by the surrounding spinal cord area.

anterior, and peroneous longus. The specific Dixon MRI parameters for the lower extremities included: TR = 6.59 ms, TE1 = 2.45 ms TE2 = 3.675 ms, flip angle = 12 degrees, bandwidth 1 = 510 bandwidth 2 = 660 Hz/Px and an imaging matrix of 448 × 266. A read field of view of 320–340 mm was used on the lower extremity muscles using a 16-channel body array surface coil, and 60 slices per slab with a slice thickness of 5 mm and a slice oversampling of 6.7% were acquired. The acquisition time was 4:12 min with a rectangular view of 60%, four averages and an in-plane resolution of 0.5 mm. Localizer scans were used to obtain the fat/water data in the axial plane perpendicular to the tibia.

Analysis of the lower extremity MRI data was performed using customized imaging analysis scripts created in MatLab (Version 2014b, MathWorks, Natick, MA, USA). One experienced researcher manually defined each region of interest (ROI) in the four leg muscle groups by contouring each muscle within its fascial borders with the co-registered fat- and water-saturated sequences. The MFI percentage is a value of fat signal intensity to fat-plus-water signal intensity, and these MFI percentages were created using the equation:

$$[\text{Relative fat signal}/(\text{relative water} + \text{relative fat signal})] \times 100$$

Sixty slices were obtained through the leg, and averages were taken over 10 consecutive slices throughout the muscle bulk of each of the four lower extremity muscles to form individual MFI percentages.³⁴

Each outline of the 4 individual lower extremity muscles yielded a CSA value. Average individual muscle CSA values 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 infiltration³⁵, using the equation:

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

Statistical analysis

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 rmCSA 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 rmCSA ($R = -0.50$, $P = 0.06$). 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

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	30	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 (mm ²)	Stronger leg rmCSA (mm ²)	Weaker plantarflexor rmCSA (mm ²)	Stronger plantarflexor rmCSA (mm ²)
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	4377.08
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 plantarflexor rmCSA ($R = 0.54$, $P = 0.04$).

Muscle fat infiltration and lower extremity muscle CSA

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.³⁶ 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

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 CSA⁵ and decreased torque production in iSCI.⁴

One surprising finding was that damage ratios were not significantly correlated with lower extremity MFI. Though denervation is one established cause of increased MFI,^{40–42} other factors such as physical in-activity,⁴³ altered metabolic function,⁴⁴ and overall weight gain⁴⁵ 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.¹⁰

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,¹⁹ 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:

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

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

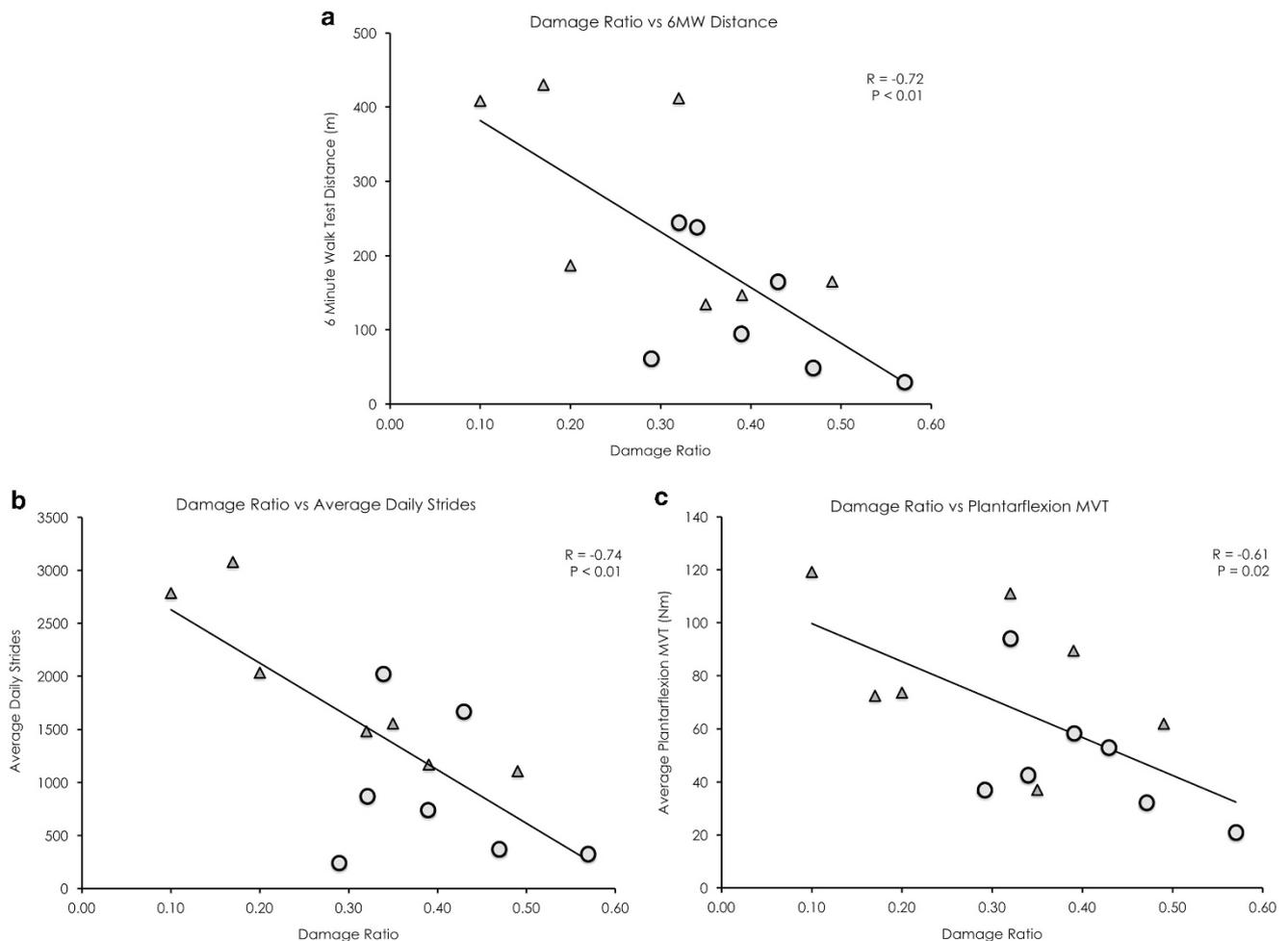


Figure 2 Damage ratios versus meters walked in 6 min (a), average daily strides (b), and isometric plantarflexion maximum voluntary torque (c). Significant negative linear correlations were found ($R = -0.72$, $P < 0.01$; $R = -0.74$, $P < 0.01$; $R = -0.61$, $P = 0.02$; respectively). Wheelchair user participants are identified as circular data points, while community ambulator participants are identified as triangular data points.

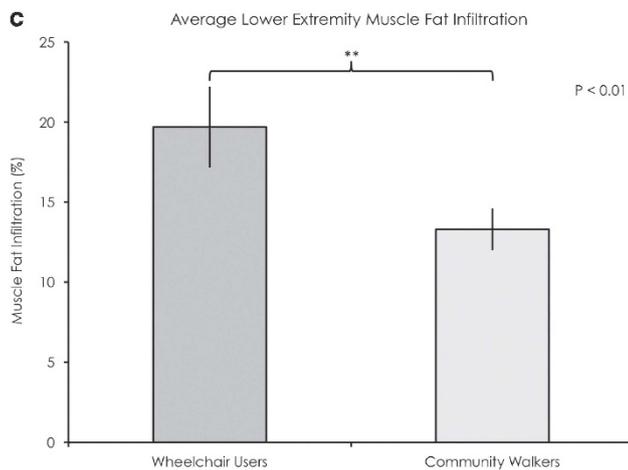
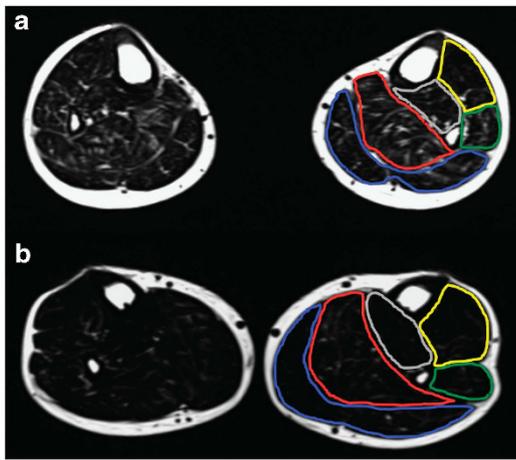


Figure 3 Cross-sectional fat-saturated images of the leg muscles in a representative wheelchair user participant (a) and a representative community walker participant (b). Outlines delineate major leg muscle groups (blue: gastrocnemius, red: soleus, yellow: tibialis anterior, green: peroneus longus). (c) A significant difference in MFI was found between groups ($P < 0.01$). Error bars denote s.e. of mean.

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.

ACKNOWLEDGEMENTS

We thank all participants for their willingness to take part in this study. We thank Mark A Hoggarth for his assistance with the MatLab programming used to analyze the MFI data, and we thank Gordhan Mahtani and Mark Connolly for their assistance with participant recruitment and data collection. JME is supported by the NIH award 1 R01HD079076-01A1, entitled 'Neuromuscular Mechanisms Underlying Poor Recovery from Whiplash Injuries'. ACS is supported by the NIH Extramural Loan Repayment Program for Clinical Researchers funded by the National Institute of Neurological Disorders and Stroke, and by the Foundation for Physical Therapy Promotion of Doctoral Studies programs. KAW is supported by the Interdisciplinary Research Training in Pain and Substance Use Disorders T32DA035165 funded by the National Institute on Drug Abuse. This research was conceptualized and carried out at Northwestern University

Table 4 Individual participant data—FIM locomotor, ASIA LEMS and WISCI II scores

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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