Published in final edited form as:

Clin Biomech (Bristol, Avon). 2015 February ; 30(2): 159–165. doi:10.1016/j.clinbiomech.2014.12.005.

Glucose uptake heterogeneity of the leg muscles is similar between patients with multiple sclerosis and healthy controls during walking

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Abstract

Background—Difficulties in ambulation are one of the main problems reported by patients with multiple sclerosis. A previous study by our research group showed increased recruitment of muscle groups during walking but the influence of skeletal muscle properties, such as muscle fiber activity, has not been fully elucidated. The purpose of this investigation was to use the novel method of calculating glucose uptake heterogeneity in the leg muscles of patients with multiple sclerosis and compare these results to healthy controls.

Methods—Eight patients with multiple sclerosis (4 men) and 8 healthy controls (4 men) performed 15 min of treadmill walking at a comfortable self-selected speed following muscle strength tests. Participants were injected with ≈ 8 millicuries of [^{18}F]-Fluorodeoxyglucose during walking after which positron emission tomography/computed tomography imaging was performed.

Findings—No differences in muscle strength were detected between multiple sclerosis and control groups ($P > 0.27$). Within the multiple sclerosis group differences in muscle volume existed between the stronger and weaker legs in the vastus lateralis, semitendinosus, and semimembranosus ($P < 0.03$). Glucose uptake heterogeneity between the groups was not different for any muscle group or individual muscle of the legs ($P > 0.16$, $P = 0.05$).

Interpretations—Patients with multiple sclerosis and healthy controls showed similar muscle fiber activity during walking. Interpretations of these results, with respect to our previous study, suggest that walking difficulties in patients with multiple sclerosis may be more associated with altered central nervous system motor patterns rather than alterations in skeletal muscle properties.

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Keywords

Positron Emission Tomography; Exercise; [^{18}F]-Fluorodeoxyglucose; Computed Tomography; Clinical Disability; Muscle fiber activity

1. Introduction

Multiple sclerosis (MS) is the leading cause of neurological disability in young adults [1]. Common symptoms include: difficulties walking, muscle weakness, and increased levels of fatigue [2, 3, 4]. Previous studies [5, 6, 7] have shown alterations in skeletal muscle properties which have been associated with declines in motor task performance and/or fatigue. These changes include: alterations in muscle fiber types [5], reduced muscle relaxation time [6], and reduction in the total number of fibers [7]. Along with the changes in skeletal muscles, alterations in the central activation of these muscles have also been reported [5, 6, 8].

Electromyography (EMG) is the traditional technique used to measure muscle activity. Intramuscular recordings and multi electrode arrays can also provide information on motor unit activity, but only for small portions of superficial muscles. Positron emission tomography (PET) with the glucose analogue [^{18}F]-Fluorodeoxyglucose (FDG) has been used to measure activity of whole muscles [9], including deep muscles not accessible by EMG. [^{18}F]-FDG uptake reveals the utilization of ordinary glucose, a major energy source for the human body. Therefore, PET with [^{18}F]-FDG can identify inefficient muscle activation strategies which may play an important role in impaired walking performance and greater fatigability in patients with MS [9, 10, 11]. PET/[^{18}F]-FDG can provide insight into muscle fiber (motor unit) activity by examining the spatial distribution of [^{18}F]-FDG within a muscle [12, 13]. This process uses the coefficient of variation of [^{18}F]-FDG uptake to estimate glucose uptake heterogeneity (GUh). As more motor units, and in turn muscles fibers are recruited, GUh decreases [12], due to the increased proportion of fibers activated within a muscle.

This technique has been previously used in young and old healthy adults [12, 13]. Heinonen et al. [12] showed that as exercise intensity increased GUh decreased within the quadriceps femoris in young adults, reflecting the recruitment of more motor units to complete higher intensity tasks. In a study of healthy older adults, Rudroff et al. [13] found that increases in GUh were consistent with motor unit remodeling that occurs with aging. Their results showed that older adults had fewer motor units which were distributed less equally throughout muscle tissue and that older men used different muscle activation strategies to perform the same task as young men. Currently there are no reports of GUh within any neuro-logical/-muscular disease populations. Utilizing this technique in these clinical populations may provide new insights into the activation and recruitment of skeletal muscle during functional tasks.

The reduction of muscle fibers [7] and the loss of lower motor neurons [14] contribute to the reduced number of motor units within a muscle in patients with MS. Fewer motor units would lead to a reduced ability to activate the working muscle homogenously during

contractions and could be a contributing factor to motor deficits and disability in patients with MS. The purpose of this study was to compare GUh in leg muscles of patients with MS and healthy controls during treadmill walking. We hypothesized that patients with MS would show greater GUh in skeletal muscles involved in ambulation compared to healthy controls reflecting alterations in muscle fiber activation and that GUh would be associated with levels of disability.

2. Methods

2.1 Participants

Eight (4 men) mildly disabled patients with the relapsing remitting MS and 8 sex matched controls were recruited from the Denver Colorado area via advertisements through the Rocky Mountain MS Center and University of Colorado – Anschutz Medical Campus study announcement newsletter. All participants signed informed consent approved by the Colorado Multiple Institutional Review Board and were in accordance with the Declaration of Helsinki. Participants were initially screened by phone interview. Requirements to participate in the study for patients with MS were: being 18 to 55 years of age, confirmed diagnosis of MS, able to walk 15 min without assistance, score of < 2 for the legs on the Modified Ashworth spasticity scale (MASS) (indicating no greater than minimal level of spasticity), and have had no changes in disease progression in the last 3 months. Main Exclusion criteria for patients with MS included: relapse within the last 3 months, history of seizures, having an unrelated condition that would exacerbate fatigue, and any medical diagnosis with contraindications to exercise participation. Eight healthy participants without neurological, muscular or skeletal disease were recruited for the control group.

2.2 Experimental protocol

Participants arrived at the Colorado Translational Research Imaging Center during the morning hours following an 8 hour fast, and patients with MS were assessed for disability levels utilizing the Patient Determined Disease Steps (PDDS). The PDDS has been validated and shows a high correlation to the Expanded Disability Status Scale (EDSS) [15, 16, 17, 18, 19]. Leg spasticity was graded using the MASS. Measurements for height, weight, comfortable walking speed, and muscle strength preceded 15 min of treadmill walking. After completion of treadmill walking participants immediately underwent PET/Computed Tomography (CT) imaging. Figure 1 is a visual representation of the experimental timeline.

2.3 MVC force

Before the walking test, each subject performed an isometric maximal voluntary contraction (MVC) with the knee extensor and knee flexor muscles of the left and right leg. MVC forces were measured with the knee and hip at 90 of flexion. The MVC task comprised a 3 s increase in force from zero to maximum with the maximal force held for ~3 s, and subjects were verbally encouraged to achieve maximal force. Subjects rested for 60 to 90 s between trials. When the peak forces achieved in two of the three trials differed by $>5\%$, additional MVCs were performed until this criterion was met. The greatest force achieved by each subject was taken as the MVC force. Lower-leg length was measured from the head of the fibula to the midpoint of the lateral malleolus. Knee extensor and flexor torque was

calculated in N·m by multiplying the recorded force in Newtons by measured lower-leg length in meters. To designate stronger and weaker legs for each group, the torques of the knee extensors and flexors were added together. The higher torque value between the legs determined the stronger leg.

2.4 Walking protocol

Following the MVC testing, participants' plasma glucose levels were tested via finger stick. This ensured that the measurement of glucose uptake began from comparable baseline conditions, and that participants did not have impaired glucose regulation. A 22 gauge i.v. catheter was placed into an antecubital vein in the subject's right arm for injection of [^{18}F]-FDG. Subjects then walked on a treadmill for 15 min at a comfortable self-selected pace. The self-selected pace was previously determined by measuring the time each participant took to walk down an 18m hallway. Three trials were performed, with the average of the two closest times being set as the initial treadmill speed. Two min after the start of the treadmill walking test, ≈ 8 mCi of [^{18}F]-FDG in 10 ml of saline was infused into the vein via the inserted catheter. Once walking began any adjustments to speed were made within the first two min. Immediately after the conclusion of treadmill walking the catheter was removed and subjects were guided into the PET/CT camera for whole body imaging utilizing a standard testing protocol used in the Colorado Translational Research Imaging Center.

2.5 PET/CT imaging and analysis

Imaging was performed with a Philips Hybrid Gemini TF 64 scanner (Philips Healthcare, Cleveland, OH, USA). CT imaging was performed first and immediately followed by PET imaging with the subject's body position secured to maintain co-registration.

Regions of interest (ROI) were drawn in the transverse plane by two investigators, confirmed in both sagittal and frontal planes, for 17 leg muscles after identification on each CT image data set using Analyze 11.0 (Analyze Direct, Rochester, MN, USA). Linear regression analysis was performed to assess inter-rater reliability between the two investigators responsible for identifying the ROIs for each muscle. The accuracy of reviewer identification of ROIs for each muscle was shown by a very high inter-rater reliability ($r^2 = 0.92$, $P < 0.01$).

Semi-automatic thresholds were set for bone, fat, and muscle tissue. Muscle tissue was identified with a Hounsfield unit (HU) range of 0–150 [21, 22], which allowed for muscle tissue to be free of intramuscular fat. Individual muscle ROIs were then created by encircling the muscle on each transaxial slice that it could be identified on (Figure 2). Individual muscles included: rectus femoris, vastus medialis, vastus intermedius, vastus lateralis, short and long heads of the biceps femoris, semimembranosus, semitendinosus, gracilis, sartorius, tensor fascia latae, iliopsoas, adductor magnus, medial and lateral heads of the gastrocnemius, soleus, and tibialis anterior. Volume calculations were performed for each ROI. Glucose uptake for each ROI was calculated as the mean standardized uptake value (SUV_{mean}), which is calculated as the mean intensity value of the ROI corrected for

time of injection, participant body weight, and injected dose. GUh was then calculated as follows: $GUh = (SD/SUV_{mean}) \times 100$, [12, 13].

2.6 Statistical analysis

Statistical analysis was performed using SPSS 22 (IBM Corp, Armonk, NY, USA). Distribution of the data was tested using the Shapiro-Wilk test. For data with a normal distribution, paired and un-paired t-tests were used to determine differences within and between groups respectively. In order to control for comparisons made between variables that were not normally distributed, a Wilcoxon-sign rank test or Mann-Whitney U test was used for comparison within and between groups, respectively. Pearson's correlations were also calculated for associations between strength and volume asymmetries between the weaker and stronger leg, as well as correlations between GUh, volume, strength, and disability levels of leg muscles. Significance was set at a level of $\alpha < 0.05$. Data are reported as mean (SD) within tables and mean SE in figures.

3. Results

3.1 Participants

Eight patients with MS and 8 healthy controls (CON) participated in the study. Patients with MS and healthy controls did not differ in age (years: 44.9 (8.6), 37.9 (8.4), $P = 0.12$), height (cm: 171 (8) and 176 (7), $P = 0.95$), or weight (kg: 78.2 (3.3), 78.2 (6.3), $P = 0.98$). Participants reported not performing more than moderate physical activity throughout the week during their phone screening. Patients with MS walked at a slower self-selected speed than the healthy controls (km/h, 1.8 (0.3) and 2.2 (0.2), $P = 0.01$). Patients with MS were classified as having low levels of disability based on their PDDS scores (Median = 2, Range = 0–4) and their median MASS score (0.9 (0.6); range = 0–1.5) [23]. Fasting glucose levels were also similar between the groups and did not indicate impaired glucose metabolism (MS 83.6 (6), CON 78.5 (8.3), mg/dL, $P = 0.38$) [22].

3.2 Glucose uptake heterogeneity

GUh was not different between the MS and CON groups for any individual muscle or muscle group ($P > 0.16$) (Figure 3, Table 1) nor were any asymmetries detected between the muscles of the strong leg and muscles of the weak leg in either group ($P = 0.05$) (Table 1).

3.3 Muscle volume

Between the MS and CON groups only the medial gastrocnemius on the weaker leg differed in volume ($P = 0.04$) (Table 2). Asymmetries in muscle volume between the muscle on the stronger and weaker leg were identified in the MS group. The differences in volume existed in the knee extensor muscle group ($P = 0.01$), vastus lateralis ($P = 0.03$), semitendinosus ($P = 0.01$), and semimembranosus ($P = 0.03$) (Figure 4a). Table 2 displays the volume of each muscle for the MS and CON groups.

3.4 Leg Strength

There were no differences between the MS and control groups in the strength of the strong leg ($P = 0.80$) or weak leg ($P = 0.27$) (Table 3). However, both groups displayed strength

asymmetries between their stronger and weaker legs ($P < 0.03$) (Table 3). The knee extensors and flexors on the stronger and weaker legs did not differ between the MS and CON groups ($P > 0.08$) (Table 3). The MS group showed asymmetries in strength between both the strong and weak leg knee extensors and strong and weak leg knee flexors ($P < 0.03$) (Table 3, PFigure 4b). The CON group only displayed asymmetries in the knee flexors (Flexors, < 0.05) (Table 3, Figure 4b). The percent difference in force and volume between the flexors of the stronger and weaker legs were strongly correlated ($R = 0.75$, $P = 0.03$) in the MS group (Figure 5). No other correlations between strength and volume asymmetries were found (MS knee extensors, $R = -0.13$, $P = 0.76$, CON knee extensors, $R = 0.04$, $P = 0.93$, CON knee flexors, $R = -0.08$, $P = 0.84$). Only the MVC torque of the weak knee flexors was significantly associated with disability levels of patients with MS ($R = -0.67$, $P = 0.04$).

4. Discussion

The purpose of this investigation was to compare GUh in patients with MS and healthy controls during walking. This is the first study to examine GUh in individuals diagnosed with a neurological disease. Our primary hypothesis that GUh would be greater in mildly disabled patients with MS compared to controls during walking was not supported by the data. The data also suggested that in low disability patients with MS, skeletal muscle properties may be similar to healthy individuals. Further, the strength of the weaker leg's knee flexor muscle group was the only variable correlated to disability levels.

Thoumie et al. [23], Kalron et al. [24], and Broekmans et al. [25] have each presented associations between strength of the knee flexor group to ambulation and disability in patients with MS. The knee flexors eccentrically slow the lower leg at the end of swing phase in the gait cycle and are involved in compensatory strategies due to somatosensory loss and balance recovery [25, 26]. When muscle strength is associated with measures of disability there may be a critical threshold at which weakness begins to play a role. In a progressive resistance training intervention by Dodd et al. [27] they were able to improve muscular strength but did not see improvements in walking performance. This could explain why only the weaker leg's knee flexor was associated with disability level. Walking performance is one of the key contributors to disability levels in the PDDS and the expanded disability status scale (EDSS).

In this sample there were no strength differences detected between patients with MS and the healthy controls. Muscle weakness is common in patients with MS, but is not always present and can vary by muscle group [22, 28, 29, 30]. Asymmetries in muscular strength have also been found, which were associated with motor task deficits [2, 13, 28, 29]. The causes for these asymmetries are not well understood at this time. In this investigation the MS group exhibited strength asymmetries in both the knee extensors and flexors, while only the knee flexors of the CON group had asymmetric strength. When comparing the muscle group asymmetries between the groups, the asymmetries were greater in patients with MS than in the healthy controls. Along with these differences in muscular strength between the stronger and weaker legs, asymmetries in muscle volume were detected between the knee extensors in patients with MS. Pearson's correlations revealed a strong correlation between the

strength and volume of the knee flexor muscle group but not the knee extensors in patients with MS. It is suggested by previous studies [23, 26] that compensatory mechanisms may contribute to a constant training effect causing one leg to hypertrophy and become stronger. Further research needs to be conducted into this area to determine the causes of these differences between stronger and weaker leg muscle groups.

Skeletal muscle GUh is the spatial distribution of [^{18}F]-FDG, which reflects the activity of muscle fibers/motor units. Motor unit loss and remodeling are present in MS, many neurological diseases, and normal aging [14, 31, 32, 33]. Investigations into GUh in young and older men, performed by Rudroff et al. [13], showed greater GUh within the knee extensors of the older men during an isometric, fatiguing contraction. They concluded that older men were unable to modulate motor units in the same manner as younger men. In the present study the data suggests that mildly disabled patients with MS and healthy individuals had similar motor unit activation strategies, evidenced by similar GUh. However, in a previous study of our research group [22], greater muscle glucose uptake was seen within the knee flexors and hip muscles of patients with MS compared with healthy subjects. Taken together with this investigation, it appears that patients with MS recruit certain muscle groups to a greater extent but are still able to use similar muscle fiber (motor unit) activation strategies, as estimated by GUh, within those muscles. These altered muscle group activation patterns, compared to healthy individuals, may play a role in increased fatigue which is often seen in patients with MS.

Ng et al. [6] looked at motor unit activity during the performance of MVC and found that patients with MS were unable to fully activate the dorsiflexor muscle group due to lack of central drive. When electrically stimulated it was found that patients with MS were able to achieve similar force output as their healthy controls. In this study muscle strength and volume were similar between the MS and CON groups, which suggests that the groups had similar neural drive. If neural drive is similar between the groups, motor unit recruitment would not be expected to be different, which may be why GUh was similar as well.

Two other factors must also be taken into consideration when comparing these results. One is that walking uses submaximal force generation. It is possible that GUh is similar between the two groups at lower force outputs but may change as the force required to perform a task increases or when high levels of performance fatigability set in. Also, the range of disability was greater in Ng et al. [6]. As individuals progress to higher levels of neurological disability, it is likely that their ability to recruit motor units will diminish and that this point may be reflected by greater GUh.

Another factor to consider is the decrease in GUh with increasing intensities during dynamic activities [12]. Patients with MS walked at lower speed, which could signify a lower intensity, although previous investigators have shown an increased cost of walking in patients with MS compared to healthy individuals [34, 35]. Due to the low levels of disability and the low intensity of self-select walking speeds, these factors would most likely not influence our results.

4.1 Methodological considerations

One limitation of this study is the relatively small sample size, although it is similar in size to previous reports on GUh [12, 13]. Another is the poor temporal resolution of PET/[¹⁸F]-FDG. Due to this fact, certain motor unit properties such as frequency modulation and rate coding cannot be ascertained. Other modalities like EMG are able to measure these properties and when used in conjunction with PET/[¹⁸F]-FDG may provide even greater information on skeletal muscle properties during task performance in patients with MS. Dynamic PET scans can be used to improve time resolution but are limited by activities that are able to be accomplished within the camera itself.

4.2 Future studies

Measuring GUh provides a unique look at muscle and muscle fiber (motor unit) activity during the performance of functional tasks. To take advantage of this fact, future studies should be conducted looking at this variable in patients with MS at greater disability levels. GUh could also present insight into the muscle activity of patients with specific alterations in functionality and/or disability. Certain alterations within the gait cycle may be due in part to the inability to properly and homogeneously activate skeletal muscles. Examining GUh in patients with MS who have altered gait mechanics may allow for new rehabilitative strategies to be implemented, help in determining the efficacy of current standards, and improved monitoring of disease progression.

4.3 Conclusion

The data suggests that the activation of muscle fibers during walking at a self-selected speed is similar between mildly disabled patients with relapsing remitting MS and healthy controls even though greater asymmetries in knee flexor strength are present. This data, in concert with previously published data by our research group [22], suggests that low levels of disability may be more directly caused by alterations in the recruitment of muscle groups and motor patterns generated within the central nervous system rather than alterations in skeletal muscle properties. Even though skeletal muscle properties may not be the most influential variables affecting low disability levels, it is still important for patients with MS to maintain active lifestyles to prevent loss of muscular strength and the onset of critical thresholds which may mark greater disability. Clinical translation of this data may come in the way of guiding physical therapists to concentrate more on full body functional activities during rehabilitative sessions to retrain/maintain motor patterns of everyday activities.

Acknowledgments

The authors would also like to thank John-Michael Benson for his help in image analysis, Dr. Jeff Hebert, Dr. Phil Koo, and Ramesh Karki at the University of Colorado, School of Medicine for their help in participant recruitment and image acquisition.

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Highlights

- We performed FDG-PET imaging on persons with and without MS.
- Muscle fiber activity was estimated by the spatial distribution of FDG.
- Skeletal muscle properties were similar between patients and controls.
- Walking ability may be more associated with muscle group activation strategies.

Figure 1.
A visual representation of the experimental procedures timeline

Figure 2.

Cross-section of corresponding lower limb PET/CT images comparing glucose uptake heterogeneity (GUh) for a person with MS and a healthy control after walking. Top: The above CT images show the designated regions of interest for individual muscles. Bottom: The lower PET images show the distribution of glucose uptake. Each color represents the glucose uptake value on a voxel by voxel basis. Red denotes the greatest signal intensity.

Figure 3.

Glucose uptake heterogeneity (GUh) of the knee extensors (RF, Rectus Femoris; VL, Vastus Lateralis; VI, Vastus Intermedius; VM, Vastus Medialis) knee flexors (BFL, Biceps Femoris Long Head; BFS, Biceps Femoris Short Head; SM, Semimembranosus; ST, Semitendinosus; Grac, Gracilis) lower leg (TA, Tibialis Anterior; GL, Gastrocnemius Lateral Head; GM, Gastrocnemius Medial Head; Sol, Soleus) and hip (TFL, Tensor Fasciae Latae; Iliop, Iliopsoas; Sart, Sartorius; AdM, Adductor Magnus) of MS and control group. No differences were detected between the MS and control groups ($P > 0.05$).

Figure 4. (A) Muscle volumes (cm³) and (B) Torques (N·m) of knee extensors and flexors of each leg for MS and CON. S, Strong; W, Weak. * = $P < 0.05$ between strong and weak legs within a group.

Figure 5. Pearson's correlation of % difference in torque and volume between the knee flexors of the strong and weak legs of patients with MS.

Table 1

Glucose Uptake heterogeneity (GUh%)

GUh (mean (SD)) for muscle groups and individual muscles. Strong and weak legs were designated based on the sum of the knee extensor and flexor torques. The spatial distribution of [¹⁸F]-FDG for the individual muscles within each leg is reported. No differences were detected between the MS and control groups for muscle groups or individual muscles or between individual muscles of strong and weak legs ($P = 0.05$).

S = Strong Leg W = Weak Leg	MS	P-Value S vs W	CON	P-Value S vs W	P-value MS vs. Con
Knee Extensors					
S_RF	21.14 (2.64)		21.22 (1.39)		0.80
W_RF	24.33 (5.10)		22.16 (3.17)		0.51
S_VL	21.09 (3.49)	0.07	22.64 (2.29)	0.67	0.28
W_VL	18.69 (2.47)		19.48 (1.79)		0.88
S_VI	18.43 (1.05)	0.67	19.57 (2.01)	0.78	0.23
W_VI	19.12 (3.44)		19.08 (1.83)		0.72
S_VM	19.86 (3.33)	0.58	19.15 (2.21)	0.67	0.51
W_VM	23.52 (2.77)		24.52 (2.67)		0.44
Knee Flexors					
S_BFL	24.05 (4.68)	0.74	23.17 (2.07)	0.26	0.65
W_BFL	19.65 (3.54)	0.05	18.47 (2.50)	0.89	0.65
S_BFS	19.60 (4.00)		20.08 (2.81)		1.00
W_BFS	19.13 (2.49)	0.48	19.16 (2.03)	0.13	0.88
S_SM	16.80 (5.02)		16.77 (3.03)		0.80
W_SM	15.71 (2.82)	0.58	15.92 (2.03)	0.67	0.72
S_ST	20.30 (4.90)		16.94 (2.95)		0.16
W_ST	18.08 (2.03)	0.07	17.97 (3.10)	0.21	0.51
S_Grac	22.12 (3.59)		20.84 (3.87)		0.51
W_Grac	20.19 (2.91)	0.07	20.62 (3.66)	1.00	0.88
S_TA	23.27 (10.15)		18.07 (4.09)		0.16
W_TA	21.33 (6.64)	0.78	18.36 (3.79)	0.33	0.57
S_GL	22.81 (6.11)		24.49 (8.19)		0.51
W_GL	24.15 (7.28)	0.21	25.90 (8.01)	0.40	0.65
	22.59 (6.89)		25.25 (8.01)		0.51
	26.17 (5.18)	0.07	29.65 (19.3)	0.78	0.44

S ₊ = Strong Leg W ₋ = Weak Leg	MS	P-Value S vs W	CON	P-Value S vs W	P-value MS vs. Con
S_GM	19.31 (4.22)		22.43 (4.53)		0.16
W_GM	24.43 (11.21)	0.48	22.21 (6.07)	0.89	0.80
S_Sol	25.29 (6.20)		26.23 (2.76)		0.57
W_Sol	24.64 (2.58)	0.78	25.93 (6.94)	0.78	0.88
S_TFL	26.09 (9.07)		24.93 (9.10)		0.72
W_TFL	26.76 (17.58)	0.78	18.54 (2.46)	0.05	0.16
S_Iliop	35.13 (10.74)		33.45 (9.31)		0.96
W_Iliop	39.81 (15.70)	0.09	31.66 (6.63)	0.23	0.65
S_Sar	24.28 (4.53)		20.94 (3.03)		0.28
W_Sar	23.99 (7.71)	0.78	23.35 (3.24)	0.09	0.44
S_AdM	29.09 (11.93)		30.57 (7.10)		0.23
W_AdM	28.03 (6.10)	0.58	29.76 (5.85)	0.78	0.51

RF, Rectus Femoris; VL, Vastus Lateralis; VI, Vastus Intermedius; VM, Vastus Medialis; BFL, Biceps Femoris Long Head; SM, Semimembranosus; ST, Semitendinosus; Grace, Gracilis; TA, Tibialis Anterior; GL, Gastrocnemius Lateral Head; GM, Gastrocnemius Medial Head; Sol, Soleus; TFL, Tensor Fasciae Latae; Iliop, Iliopsoas; Sart, Sartorius; AdM, Adductor Magnus.

Table 2

Muscle volumes (cm³)

Muscle volume (cm³) (mean (SD) for muscle groups and individual muscles. Strong and weak legs were designated based on the sum of the knee extensor and flexor torques. Volumes were calculated using Analyze 11.0 for each ROI.

S_ = Strong Leg W_ = Weak Leg	MS	P-Value S vs W	CON	P-Value S vs W	P-value MS vs. Con
Knee Extensors					
S_RF	371.24 (113.61)		461.06 (177.98)		.33
W_RF	216.27 (76.95)		247.51 (95.36)		.65
S_VL	208.10 (71.58)	.12	252.50 (92.26)	.40	.44
W_VL*	561.12 (154.58)		654.18 (281.04)		.57
S_VI	502.70 (157.72)	.03	691.82 (274.38)	.21	.16
W_VI	356.28 (152.05)		399.83 (189.34)		.65
S_VM	348.19 (158.60)	.40	414.24 (162.30)	.58	.44
W_VM	397.94 (106.44)		504.44 (184.40)		.20
S_BFL	379.33 (105.94)	.12	523.99 (205.13)	.12	.16
W_BFL	131.81 (35.90)		140.77 (36.68)		.80
S_BFS	185.33 (62.08)		194.03 (63.06)		.72
W_BFS	165.58 (46.59)	.09	194.40 (59.78)	.78	.38
S_SM	57.11 (15.75)	.89	72.75 (26.71)	.48	.20
W_SM*	58.37 (14.07)		67.53 (23.19)		.38
S_ST	215.37 (44.13)	.03	183.74 (36.00)	.05	.16
W_ST*	199.50 (48.07)		200.71 (46.18)		.96
S_Grac	150.57 (59.97)		154.50 (42.72)		1.00
W_Grac	130.73 (52.80)	.01	179.19 (98.20)	1.00	.33
S_TA	76.26 (28.36)		81.27 (31.52)		.72
W_TA	79.33 (28.73)	.40	79.56 (28.39)	.58	1.00
S_GL	105.98 (24.38)		119.35 (30.08)		.44
W_GL	108.64 (28.93)	.78	112.65 (29.76)	.07	.72
S_GM	243.74 (87.40)		215.35 (38.09)		.44
W_GM	226.70 (78.13)	.07	238.22 (56.16)	.16	.88
S_GM	211.21 (37.52)		255.05 (58.43)		.13

S ₊ = Strong Leg W ₋ = Weak Leg	MS	P-Value S vs W	CON	P-Value S vs W	P-value MS vs. Con
W_GM [†]	197.37 (43.35)	.33	253.70 (49.44)	.89	.04
S_Sol	360.68 (148.22)		420.77 (106.38)		.28
W_Sol	346.91 (148.15)	.67	395.95 (120.24)	.09	.23
S_TFL	52.44 (28.17)		58.43 (29.53)		.65
W_TFL	47.48 (25.29)	.21	59.41 (25.41)	.78	.33
S_Iliop	311.04 (113.26)		349.99 (132.68)		.51
W_Iliop	297.74 (75.96)	.58	365.51 (114.34)	.16	.16
S_Sart	120.14 (45.84)		156.03 (59.05)		.16
W_Sart	106.53 (39.04)	.05	157.91 (67.90)	.58	.13
S_AdM	521.40 (166.26)		589.04 (304.91)		.88
W_AdM	470.86 (140.85)	.16	588.73 (285.72)	.40	.51

[†] = $P < 0.05$ between MS and CON.

* = $P < 0.05$ between legs.

RF, Rectus Femoris; VL, Vastus Lateralis; VI, Vastus Intermedius; VM, Vastus Medialis; BFL, Biceps Femoris Long Head; BFS, Biceps Femoris Short Head; SM, Semimembranosus; ST, Semitendinosus; Grace, Gracilis; TA, Tibialis Anterior; GL, Gastrocnemius Lateral Head; GM, Gastrocnemius Medial Head; Sol, Soleus; TFL, Tensor Fasciae Latae; Iliop, Iliopsoas; Sart, Sartorius; AdM, Adductor Magnus.

Table 3

Leg Strength (N·m)

Leg strength (N·m) (mean SD) for muscle groups. Strong and weak legs were designated based on the sum of the knee extensor and flexor torques.

S_ W_ = Strong Leg = Weak Leg	MS	P-Value S vs W	CON	P-Value S vs W	P-value MS vs. Con
S_Leg	199.19 (64.64)		207.58 (67.07)		0.80
W_Leg*	160.83 (44.96)	0.01	193.18 (65.49)	0.03	0.27
S_Knee_Extensors	136.33 (47.05)		149.67 (53.18)		0.60
W_Knee_Extensors*	118.02 (39.120)	0.03	138.82 (52.74)	0.09	0.39
S_Knee_Flexors	62.86 (22.46)		57.91 (14.99)		0.61
W_Knee_Flexors*	42.81 (9.87)	0.01	54.36 (14.34)	< 0.05	0.08

* = $P < 0.05$ between legs.