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Neuromuscular Electrical Stimulation Compared to Volitional Exercise in Improving Muscle Function in Rheumatoid Arthritis: A Randomized Pilot Study

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Abstract

Objectives—To compare the feasibility and effectiveness of Neuromuscular Electrical Stimulation (NMES) with high-intensity volitional resistance training in improving muscle structure and function, and physical function in patients with rheumatoid arthritis (RA). We also described pre- and post-intervention values of myocyte characteristics.

Methods—Two-group single-blinded pilot randomized study in adults with RA. Participants were assigned to 36 sessions over 16 weeks of NMES (n=31) or volitional training (n=28). Outcome measures included muscle structure and function (quadriceps muscles area, density, and strength), physical function (performance-based and patient-reported), feasibility (pain, disease activity, attrition, and adherence), and myocyte characteristics (area, proportion of type I or II muscle fibers, and intramyocellular lipid content). Analysis of covariance was used to compare groups.

Results—The intervention intensity for the NMES group was less than half of the volitional group (31% vs. 77% of maximum effort). Both groups experienced significant improvements in muscle structure and function (p values from $<.001$ to $.019$). Improvements in muscle characteristics and physical function were not different between groups. Exercises did not result in serious adverse events or increases in pain and disease activity. Attrition was 29% in NMES and 7% in volitional groups.

Conclusions—Both NMES and high-intensity volitional resistance training can be used as effective approaches to improve muscle structure and function in RA. NMES may be a viable alternative to promote muscle function for patients in whom high-intensity resistance exercise may not be tolerated or is contra-indicated, but attrition needs to be considered when using this approach.

Nearly two-thirds of patients with rheumatoid arthritis (RA) experience some level of muscle atrophy.(1) Reversing muscle atrophy in RA is important not only to improve

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performance during daily tasks, but also to increase the capacity of muscles to store protein. Muscle protein plays a crucial role in enabling adaptation to metabolic stresses and fight infections(1–4). Serious infections are a major concern in patients with RA and contribute to overall mortality(5). Therefore, promoting muscle hypertrophy may ultimately contribute to improved health in RA(4).

Volitional resistance exercise is typically the first countermeasure against muscle atrophy. Studies on resistance exercise in RA have demonstrated significant improvements in muscle strength and physical function without parallel increases in muscle size(6–12), suggesting that this population might be resistant to the anabolic effects of exercise(10). The few studies that demonstrated muscle hypertrophy in RA used resistance training at high-intensity, representing approximately 80% of the maximum load an individual can tolerate(13, 14). In patients with RA, pain and disability due to disease activity may reduce tolerance to high-intensity resistance exercises and alternative approaches to promote muscle hypertrophy should be explored.

Neuromuscular electrical stimulation (NMES) is one such alternative method that incorporates the use of electrical current to activate skeletal muscles and produce contractions(15). NMES recruits motor units in a non-selective pattern of activation, where both slow and fast-twitch fibers are activated at once, unlike volitional contractions, where slow-twitch fibers are activated first and fast-twitch fibers are recruited only with near maximal effort(16–19). Thus, one clinical advantage of NMES over volitional exercise is the potential to activate all muscle fibers at relatively lower contraction intensities, which may make this approach particularly effective to reverse muscle atrophy in RA that seems to predominantly affect type II fibers(20, 21).

NMES has been shown to promote muscle hypertrophy in a variety of patient populations(22–25). Our preliminary work indicated that NMES is a promising intervention to enhance muscle mass and strength in RA; however, NMES was tested in a small series of patients and randomized studies are needed to assess the effectiveness of NMES in this population(26). To that end, the primary objective of this study was to compare the effects of NMES and volitional resistance training on muscle structure and function (hypertrophy, strength, density) and physical function (performance-based and patient-reported outcomes) in patients with RA. The secondary objective was to determine the safety and feasibility of using NMES. The descriptive objective was to characterize pre- and post-intervention myocyte area, the proportion of type I or II muscle fibers, and intramyocellular lipid content.

PATIENTS AND METHODS

This was a two-group single-blinded pilot randomized study of parallel design implemented from Dec/2009 to Dec/2013 in the Department of Physical Therapy, University of Pittsburgh. Participants were enrolled if they were older than 21 years of age, diagnosed with RA for >5 years by a rheumatologist as per the American College of Rheumatology criteria, fluent in English, and able to ambulate independently without an assistive device. Exclusion criteria included cardiovascular disease, uncontrolled hypertension, neurological or muscular conditions, history of quadriceps/patellar tendon rupture or adverse reaction to

electrical stimulation, participation in resistance training 2 times/week, change in RA medication in the month prior, cholesterol-lowering medication use, malignancy, and pregnancy. Individuals with <70 degrees of knee flexion were excluded to enable proper positioning on the isokinetic dynamometer.

Recruitment and Consent

Subjects were recruited through letters sent from their rheumatologists, the University of Pittsburgh Medical Center Arthritis Network Registry, and public announcements. The University of Pittsburgh Institutional Review Board approved the study protocol (PRO08090141). All participants provided written informed consent.

Randomization and Interventions

A statistician generated the randomization sequence and the research coordinator, not involved with testing/treatment, randomized the participants through a web-based computer system after the baseline visit. Allocation ratio was 1:1 to NMES or volitional exercise training. The testers were masked to group assignment. While participants could not be masked to treatment assignment, they were instructed not to discuss treatment with the testers. Physical therapists masked to participants' performance on outcome measures delivered the interventions.

The groups participated in 2 to 3 exercise sessions/week, for a total of 36 exercise sessions over 16 weeks. Both legs were targeted for training. The interventions adhered to the best evidence-based practice, meaning that the NMES was administered at maximum tolerance while the volitional training was applied at high-intensity (15, 27, 28). Each exercise session started with warm-up comprised by 5 minutes of stationary cycling without resistance and 1–2 bouts of 30-sec quadriceps stretching.

NMES Training was administered using an Infinity Plus portable NMES unit (Empi, 599 Cardigan Road, St. Paul, MN). Stimulus parameters were based on previous and included a pulse rate of 75 pulses/second and pulse duration of 450 microseconds (15, 26). Stimulus on/off time was 12-sec on (3-sec ramp up, 6-sec full contraction, 3-sec ramp down), and 48-sec off to minimize muscle fatigue (1-min cycle). The skin areas for the electrodes were rubbed with alcohol. Two 6.9 cm by 12.7 cm self-adhesive electrodes (Dura-Stick, Chattanooga Corp., Chattanooga, TN, USA) were placed on the skin, one proximal over the vastus lateralis and one distal over the vastus medialis. Participants were instructed not to voluntarily contract their muscles and let the stimulator do the work. A total of 15 electrically elicited contractions were applied. The amperage of the NMES unit was gradually increased as tolerated during each session. To help participants tolerate the NMES, we used coping strategies such as ignoring pain and distraction (e.g., engaging in conversation or asking the subjects to visualize something pleasant) (29). The intensity of NMES was calculated in percentage as the torque generated during the NMES contraction divided by the torque generated during a maximum volitional isometric contraction (MVIC). The MVIC torque output (Nm) of the quadriceps muscles was assessed using an isokinetic dynamometer (Biodex System 3 Pro, Shirley, NY) as described before (26). NMES torque output during training was determined with participants seated on the same dynamometer's

chair used to test MVIC. LabVIEW software (National Instruments, Austin, TX) was used to determine the NMES intensity, which was calculated for each exercise session and averaged across all sessions.

Volitional training was done with exercise equipment and based on best evidence(9–11). The exercises targeted mainly the quadriceps muscles and included leg extension and leg press exercises on the respective machines. Prior to training, the tester assessed the participants' one-repetition maximum (1-RM) for leg extension and leg press. Volitional training was performed in a pain-free range and consisted of 15 repetitions of each exercise with 40% load, followed by 3 sets of 8 repetitions with a load of 80% of 1-RM. Each contraction was timed for 2-sec concentric load, 2-sec eccentric load, and 3-sec interval between contractions. A 2-min rest was provided between each set. The intensity of volitional training was calculated in percentage as the force produced during each repetition of the exercises divided by the force produced during 1-RM test. The intensity was calculated for each exercise session and averaged across all sessions for each participant.

To maintain exercise intensity in the volitional group at 80% of 1-RM and concurrently consider the expected increase in muscle strength during physical training, participants repeated the 1-RM test every 4 visits, and the exercise dose was re-calculated based on new 1-RM value. In the NMES group, the MVIC testing was also performed every 4 visits. Although exercise was prescribed at maximal tolerance in the NMES group irrespective of maximal effort, the MVIC test was repeated in the same time interval as the volitional group to balance both groups on the number of maximum strength tests.

The NMES and volitional programs were designed with comparable time (attention) demands. NMES sessions (without MVIC testing) took approximately 45 minutes (15 min NMES on each side plus 15 min of set-up time for dynamometer and NMES devices). The volitional sessions (without 1-RM testing) were also 45 minutes (11 min for leg extension machine in each leg, 6 min in the leg-press for each leg, and 11 min set-up time).

Outcome Measures were assessed at baseline and 4 months after randomization and included quadriceps muscle structure and function, physical function, feasibility, and myocyte characteristics. Primary outcomes included muscle area and performance-based physical function.

Quadriceps muscle structure was assessed by muscle area and density using a mid-thigh Computerized Tomography (CT) as previously described(30). Briefly, a 10-mm thick axial image of the mid-thigh region was obtained at the femoral mid-point. Scanning parameters were 120kVp and 200–250mA, and subjects were positioned in supine in neutral position. CT images were processed using the Slice-O-Matic software that differentiates between muscle, fat, and bone tissue based on their density measured in Hounsfield Units (HU), with water as the reference at 0 HU. Muscle density ranges between 0 to 100 HU (higher values correspond to lower lipid content and better muscle quality) while adipose tissue density ranges between –190 to –30 HU. The average muscle density in HU and muscle cross-sectional area (square centimeters) were obtained. This method is reliable and valid(31). Quadriceps muscle function was assessed as muscle strength using the MVIC test(32). In

short, participants sat on an isokinetic dynamometer (Biodex, Inc) with the knee at 70° of flexion and performed five trials of isometric knee extension. The torque generated during the highest three trials was averaged.

Physical function was measured by a battery of performance-based tests and patient-reported outcomes. Performance-based tests included: (1) self-selected gait speed performed in a 4-meter pathway, (2) timed-chair stand, which involved timing 5 repetitions of rising to a full upright position and sitting back down in a chair, (3) single-leg-stance, which entails timing participants balancing on one leg while keeping their hands on the waist (average of 3 trials per leg), and (4) stair climbing, where subjects are timed while climbing up 11 steps using the handrail on the preferred side. These tests are reliable and responsive to exercise interventions(33–36). Patient-reported outcomes included the Lower Extremity Function Scale (LEFS) and the Health Assessment Questionnaire Disability Index (HAQ-DI). The LEFS is a valid instrument that queries patient's performance on 20 general daily activities. Its score ranges from 0–80, with higher scores representing better function(37). The HAQ-DI is valid and widely used in RA. It queries 20 activities of daily living and the scores range from 0 (functional disability) to 3 (severe functional disability)(38).

Measures of feasibility were leg pain (numeric rating scale from 0 to 10), disease activity (assessed by the Disease Activity Scale - DAS28 and Erythrocyte Sedimentation Rate)(39), attrition (participants who completed the 4-month assessment over participants randomized to each group), adherence (number of intervention sessions attended over the 36 prescribed), and adverse events. The occurrence of adverse events during study participation was queried during the 4-month assessment. The interventionists also documented discomfort or change in health status during each intervention session.

In a subset of participants who agreed to undergo quadriceps muscle biopsy, the following outcome measures were assessed for descriptive purposes: 1) myocyte area (for all muscle fibers, for high oxidative- type I fibers, and for low oxidative- type II fibers); 2) intramyocellular lipid (IMCL) content (for all muscle fibers and for fibers type I and type II); and 3) proportion of type I and type II muscle fibers. Description of biopsy and histochemical methods is in Appendix 1.

Sample Size and Statistical Analyses

We predetermined that with a sample size of 27 subjects per group, the study would have 80% power (two-sided $\alpha = 0.05$) to detect a 2.1 cm² difference between groups in muscle area at 4 months (SD of 2.74 cm² (26)). Accounting for 10% attrition, the target recruitment was 30 subjects per group.

We planned a priori to adjust baseline participants' characteristics in the analysis if they were considered different by clinical relevance rather than statistical significance. Within group pre-post changes were assessed by paired t-tests. To obtain adjusted comparison of continuous outcomes between treatment arms, we fitted an analysis of covariance model using baseline to follow-up change in each outcome as the response variable; treatment arm as the main factor of interest; and adjusted for potential baseline characteristics. All tests were two-sided with $\alpha = 0.05$ and were not corrected for multiple comparisons to minimize

Type 2 error. Analyses for the primary aim used intention-to-treat and per-protocol approaches. For the descriptive aim, we characterized the pre-post values of myocyte area, fiber type distribution, and IMCL content by intervention arm using boxplots. Hypothesis testing was not performed for this aim. IBM-SPSS version 23 was used for all plots and calculations.

RESULTS

From the 332 individuals who contacted the research group, 156 demonstrated interest to participate and were screened for eligibility over the phone (Figure 1). From those, 60 were eligible and invited for baseline testing, resulting in 59 participants randomized, 31 in NMES group and 28 in volitional group. 24 and 26 participants completed the study in NMES and volitional groups respectively (drop-out reasons are reported in Figure 1).

The baseline characteristics were clinically important differences between groups for age and body weight (Table 1). Clinically important differences were also observed in some outcome measures at baseline (Table 2). Thus, between-group comparisons were adjusted for baseline values of outcomes, age, and weight.

The within-group changes (from pre- to post-intervention) for muscle structure and function demonstrated statistically significant improvements in all outcome measures in both groups (p -values from $<.001$ to $.019$) (Table 2). Quadriceps muscle area increased 3.60cm^2 on average for both legs (3.9cm^2 right side, 3.3cm^2 left side) in NMES and 2.65cm^2 (2.8cm^2 right, 2.5cm^2 left) in the volitional group. Muscle density increased 1.55HU (1.5HU right; 1.6HU left) in NMES group and 1.65HU (1.8HU right, 1.5HU left) in the volitional group. Muscle strength increased on average 14 Nm in both the NMES and volitional groups. The between-group differences were not statistically significant.

The within-group changes for performance-based physical function were only significant for stair climbing (shortened 0.3 sec , $p=.034$) and chair rise (shortened 1.2 sec , $p=.024$) tests in the volitional group (Table 2). For the patient reported outcomes, the only significant within-group change was an increase in 4.2 points in the LEFS ($p=.001$) in the NMES group. None of the between-group differences in physical function were statistically significant.

Feasibility analysis demonstrated that changes in leg pain (-0.2 in NMES and -0.6 in volitional, $p=.620$) and disease activity per DAS-28 (-0.6 in NMES and -0.3 in volitional, $p=.537$) were not different between groups. There were no serious adverse events related to study participation. Minor expected adverse events due to exercise participation included muscle soreness and joint pain, but these resolved within days or weeks without requiring medical attention. Participants attended a similar number of exercise sessions, with a median adherence (Q25, Q75) of 36 (18, 36) for NMES and 36 (34, 36) for volitional (Wilcoxon $p=.0100$). Attrition was 29% in the NMES and 7% in the volitional group; which was not significant (Chi-square: 2.71 , $p=0.100$). The average intervention intensity across all treatment sessions for the NMES group was $30\pm 19\%$ of MVIC on the right and $31\pm 18\%$ of MVIC on the left leg. The volitional group exercise intensity was $77\pm 5\%$ of 1-RM on the right and $76\pm 4\%$ of 1-RM on the left leg.

For the descriptive aim, 17 participants in each group agreed to undergo quadriceps muscle biopsy pre- and post-intervention. The average number of muscle fibers examined pre-intervention was 127 (95% CI 108; 145) and post-intervention 118 (95% CI 105; 132). The changes in proportion of muscle fibers from pre-to-post intervention were negligible. Before intervention, the proportions of Type I and Type II muscle fibers in the NMES group were 63% and 37% respectively. Post-intervention they were 60% and 40% respectively. In the volitional group, the proportions of Type I and Type II muscle fibers before intervention were 53% and 47% respectively; and post-intervention they were 52% and 48%.

Myocyte area of fibers Type I and II combined increased slightly in both groups. Although the interquartile (IQ) ranges stayed essentially unchanged for the NMES group and had a slight upward shift in the volitional group, the increase in medians from pre-post-intervention did not appear to be different between groups (276 [3700 minus 3424] μm^2 in NMES and 273 [3103 minus 2830] μm^2 in volitional) (Figure 2, panel A). The changes in the NMES group seem mainly due to increases in area of type II fibers; whereas in the volitional group, the changes seem due to increases in both type I and II fibers (Figure 2, panels B and C).

IMCL for combined type I and type II muscle fibers decreased slightly in both groups. The pre-post change in IQ ranges for IMCL seemed to be more pronounced in the NMES group compared to the volitional group, with changes of -712 (4740 minus 5452) arbitrary units (AU) in the NMES group and -31 (4786 minus 4817) AU in the volitional group (Figure 3, panel A). These changes seem to be driven by different effects of each intervention on fiber phenotype. In the volitional group, decreases in IMCL were mainly observed in type I fibers, whereas in the NMES group they were observed in type I and II fibers (Figure 3, panels B and C).

DISCUSSION

This is the first study in RA to demonstrate no differences in the effectiveness of NMES and volitional exercises on quadriceps muscle area, strength, and density. The increases in muscle area were 7% in NMES and 6% in volitional groups, which were similar to improvements reported in previous studies in RA (6 to 8%) that used comparable high-intensity volitional training(13, 14, 28), and slightly less than studies in old and young healthy individuals (10 to 11%) that used comparable volitional training(40, 41). The changes in muscle quality of around 3% in both groups are slightly less than in healthy older adults (5%)(42). Lower gains in muscle area and quality in patients with RA compared to healthy population is probably due to the hypermetabolic state that makes RA patients more resistant to the anabolic effects of exercise(10, 28). The gains in muscle strength in NMES and volitional groups were 10% and 9% respectively, which are similar to improvements reported in healthy adults (10%)(40, 41) but lower than other studies in RA that used high-intensity training (25%)(14, 28). Larger gains in muscle strength in previous studies in RA are probably because their exercise training was of 24 weeks duration (14, 28), versus 16 weeks in this study and 12 weeks in studies in healthy adults(40, 41). Of note, the improvements in muscle function in this study should be put in the context that patients with RA who do not exercise lose approximately 0.7% of lean muscle mass and 2% of muscle

strength annually(27, 28). Thus, both NMES and high-intensity volitional resistance training can be used as effective approaches to improve muscle structure and function in patients with RA.

Despite similar improvement in muscle function in both groups, the average intensity of the NMES was less than half the intensity of volitional training (30.5% and 76.5% of maximum effort respectively), which is a novel finding. This observation supports the notion that NMES affects muscle function at relatively lower contraction intensities than volitional exercise(17), which is probably due to their different pattern of muscle activation. Volitional contractions follow the Henneman's size principle, where under load, the smallest motoneurons (supplying type I fibers) are activated first, and type II fibers are activated last, and only reach their maximum force production near maximal contractions(43). On the other hand, NMES is generally delivered at frequencies higher than the firing frequencies of muscles fibers, which overrides the central nervous system recruitment patterns and causes synchronous activation of all motor units within the field of current(16, 17, 44, 45). Because NMES improves muscle function at lower intensities than volitional training, it could be a viable alternative to promote muscle function in patients for whom high-intensity resistance exercise may not be tolerated or is contra-indicated.

An unexpected finding was that while both interventions improved muscle structure and function, those improvements barely influenced physical function. Explanation of this finding is twofold. First, the exercise training for both intervention arms mainly targeted the knee extensor muscles. Yet, the knee extensors contribute only to a small to moderate degree to the functional activities tested in this study.(46–48) Second, the exercise programs lacked specificity. The principle of training specificity holds that to become better at a skill, one must perform that skill. To that end, the only exercises that used similar skills as the performance-based tests were the ones from the volitional group (i.e., leg press and knee extension), which aligned with the skills required for climbing stairs and standing from a chair.

Both exercise training regimens did not result in adverse events or increased pain or disease activity. On the contrary, there was a small decrease in pain (–0.4 points, 14%) and disease activity (–0.5, 16%) in both groups. While attrition was three-fold (22%) higher in NMES than in the volitional group, the majority (71%) of participants in the NMES group tolerated the intervention well. Because both interventions were administered under similar conditions (i.e., setting, interventionist, time commitment) and the groups were similar on characteristics related to attrition (education and employment status(29)), we speculate the higher attrition in NMES group was not due to study or participant factors, but rather due to the discomfort from the noxious electrical stimulation.

Based on previous suggestions that NMES could have a preferred effect on type II muscle fibers(44, 49), this study also sought to describe the effects of interventions on muscle phenotype. This is particularly relevant in RA where muscle atrophy seems to predominantly affect type II fibers(20, 21). The findings suggest that increases in muscle area in NMES group seem predominant in type II fibers whereas in the volitional group both types of muscle fibers increase similarly. These findings need further validation in larger samples

along with the assessment of the clinical relevance of selective hypertrophy of muscle phenotypes.

A limitation of this pilot study includes small sample size. While differences between groups in muscle and physical function were very small and would likely not be significant with a larger sample, attrition was three times higher in NMES group and differences would be significant with a larger sample. Moreover, participants that dropped-out also attended few sessions of NMES. Thus, attrition and adherence are concerns when using NMES. The small sample also resulted in unbalances between groups in some baseline characteristics, which despite being adjusted in the analyses, could still have influenced the results. Additionally, the participants were not blinded to group assignment, which would be difficult to do given the very different nature of the interventions. Last, this study included subjects with moderate disease activity and mild functional limitations and the results may not be generalizable to RA populations that have severe disease and are more debilitated.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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SIGNIFICANCE AND INNOVATIONS

- Muscle atrophy is prevalent and associated with morbidity in rheumatoid arthritis (RA). While high-intensity volitional exercise is typically the first countermeasure against muscle atrophy, patients with RA might be more resistant to the anabolic effects of exercise. Neuromuscular electrical stimulation (NMES) appears to activate all muscle fibers at relatively lower contraction intensities and could be an alternative to high-intensity volitional resistance training.
- This is the first randomized study to compare NMES with high-intensity resistance training in individuals with RA. The results have shown that both NMES and high-intensity volitional resistance training can be used as effective approaches to improve muscle structure and function in RA.
- NMES improves muscle structure and function at lower training intensity compared to high-intensity resistance training and may be a viable alternative for patients in whom high-intensity resistance exercise may not be tolerated or is contra-indicated.

Figure 1.
Study Flow Diagram

Figure 2.

Boxplots of Myocyte Fiber Area Pre- and Post-Intervention.

Panel A shows pre- and post-intervention data for NMES and volitional groups for myocyte area in type I and II fibers combined. Panel B shows pre- and post-intervention data for NMES and volitional groups for area of type I fibers. Panel C shows pre- and post-intervention data for NMES and volitional groups for area of type II fibers. Light gray boxes are pre-intervention data and dark gray boxes are post-intervention data. Sample size is 17 in NMES and 17 in volitional groups. The boxes represent the interquartile (IQ) ranges and contain the median (line across the boxes). The whiskers are the highest and lowest values no greater than 1.5 times the IQ ranges. Outliers represented by circles are cases with values between 1.5 and 3 times the IQ ranges, whereas outlier represented by stars are cases with values more than 3 times the IQ range.

Figure 3.

Boxplots of Intramyocellular Lipid Pre- and Post-Intervention.

Panel A shows pre- and post-intervention data for NMES and volitional groups for intramyocellular lipid (IMCL) (arbitrary units- AU) for type I and II fibers combined. Panel B shows pre- and post-intervention data for NMES and volitional groups for IMCL of type I fibers. Panel C shows pre- and post-intervention data for NMES and volitional groups for IMCL of type II fibers. Light gray boxes are pre-intervention data and dark gray boxes are post-intervention data. Sample size is 17 in NMES and 17 in volitional groups. The boxes represent the interquartile (IQ) ranges and contain the median (line across the boxes). The whiskers are the highest and lowest values no greater than 1.5 times the IQ ranges. Outliers represented by circles are cases with values between 1.5 and 3 times the IQ ranges, whereas outlier represented by stars are cases with values more than 3 times the IQ range.

Table 1

Baseline Demographics and Clinical Characteristics of Participants

	NMES N = 31	Volitional N = 28
Age in years, mean (SD)	57.2 (8.6)	61.0 (11.0)
Females, n (%)	25 (81)	23 (82)
Height (cm), mean (SD)	165.2 (8.5)	164.5 (8.1)
Weight (kg), mean (SD)	88.1 (20.4)	81.1 (22.1)
BMI in kg/m ² , mean (SD)	32.4 (7.1)	29.8 (7.2)
Race, n (%)		
White	27 (87)	22 (79)
Black	4 (13)	6 (21)
Hispanic, n (%)	0	1 (4)
Education, n (%)		
High school or less	9 (29)	6 (21)
Attended college	22 (71)	22 (79)
Employed, n (%)	12 (39)	13 (46)
Smoker, n (%)	4 (13)	5 (18)
Disease duration (years), mean (SD)	14.2 (10.7)	17.1 (11.0)
Disease Activity		
DAS-28, mean (SD)	4.1 (1.3)	3.8 (1.1)
ESR, mean (SD)	23.2 (16.1)	28.4 (19.7)
Leg pain – 0 to 10, mean (SD)	2.8 (2.7)	3.2 (2.7)

DAS = Disease Activity Scale; ESR = Erythrocyte Sedimentation Rate

Table 2

Changes in Outcome over Time in NMES and Volitional Groups

	NMES (n = 24)			Volitional (n = 26)			Non-Imputed		Imputed [†]	
	Pre Mean (SD)	Post Mean (SD)	Change Mean (SD)	Pre Mean (SD)	Post Mean (SD)	Change Mean (SD)	Adjusted [†] Between-Groups Difference (SE)	Between-Groups P value	Adjusted [†] Between-Groups Difference (SE)	Between-Groups P value
Muscle Structure and Function										
Right-Quadriceps area (cm2)	49.0 (8.2)	52.9 (8.6)	3.9 (2.4) ***	45.2 (15.7)	48.0 (16.3)	2.8 (3.4) ***	1.1 (0.9)	.209	1.2 (0.9)	.168
Left-Quadriceps area (cm2)	48.6 (9.0)	51.9 (8.6)	3.3 (3.2) ***	46.4 (15.6)	48.9 (16.9)	2.5 (3.2) ***	0.6 (0.9)	.482	0.7 (0.9)	.445
Right-Quad attenuation (HU)	45.7 (4.6)	47.2 (5.4)	1.5 (2.3) **	45.4 (5.4)	47.2 (4.9)	1.8 (2.0) ***	−0.2 (0.6)	.745	−0.2 (0.6)	.770
Left-Quad attenuation (HU)	46.1 (4.7)	47.7 (4.9)	1.6 (2.4) **	46.4 (4.6)	47.9 (4.9)	1.5 (3.1) *	−0.3 (0.7)	.674	0.1 (0.8)	.860
Right-MVIC (Nm)	145 (32)	160 (35)	15 (20) **	143 (65)	158 (68)	15 (14) ***	−0.5 (5.2)	.924	−0.3 (5.1)	.953
Left-MVIC (Nm)	144 (37)	157 (39)	13 (20) **	148 (64)	161 (70)	13 (19) **	−2.1 (5.8)	.719	−1.2 (5.9)	.838
Performance-based Physical Function										
Stair climbing test (sec)	6.6 (3.2)	6.2 (2.4)	−0.4 (2.1)	7.0 (2.7)	6.7 (2.4)	−0.3 (0.8) *	−0.3 (0.4)	.470	−0.2 (0.4)	.567
Timed chair stand (sec)	14.7 (8.0)	13.3 (7.3)	−1.4 (5.3)	12.6 (3.3)	11.4 (3.2)	−1.2 (2.4) *	0.5 (1.0)	.620	0.4 (1.0)	.657
Gait speed (m/sec)	1.07 (.28)	1.07 (.23)	0.00 (.19)	1.09 (.23)	1.10 (.21)	0.01 (.19)	0.004 (0.05)	.942	−0.0001 (0.05)	.998
Right-Single leg stance (sec)	15.3 (12.1)	16.1 (11.4)	0.8 (4.7)	10.6 (9.8)	12.4 (11.0)	1.8 (4.8)	−0.4 (1.3)	.770	0.05 (1.4)	.972
Left-Single leg stance (sec)	17.8 (12.1)	17.7 (8.7)	−0.1 (6.7)	11.7 (11.3)	14.2 (9.7)	2.5 (6.5)	−0.2 (1.8)	.896	−0.6 (1.7)	.752
Patient Reported Outcomes of Physical Function										
LEFS	54.0 (18.0)	58.2 (17.0)	4.3 (5.5) **	58.8 (12.2)	58.1 (13.2)	−0.7 (10.3)	4.2 (2.4)	.087	4.3 (2.4)	.078
HAQ	0.86 (0.59)	0.80 (0.63)	−0.05 (.22)	0.74 (0.61)	0.69 (0.64)	−0.05 (0.40)	−0.01 (0.1)	.926	−0.03 (0.09)	.754

HU=Hounsfield Units, MVIC=Maximum Voluntary Isometric Contraction; LEFS= Lower Extremity Functional Scale; HAQ= Health Assessment Questionnaire. Non-Imputed analyses (complete cases only) have 24 and 26 observations in NMES and Volitional groups respectively. Imputed analyses have 31 and 28 observations in NMES and Volitional groups.

[†]Multiple Imputation Procedure done in SAS v.9.4 using Markov chain Monte Carlo and Expectation Maximization (MCMC-EM) method.

[‡]Analyses adjusted by age, weight, and baseline values of the outcome.

^{*}Significant at $\alpha < 0.05$;

^{**}Significant at $\alpha < 0.01$;

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Significant at $\alpha < 0.001$.
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