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Effect of High-Intensity Exercise on Multiple Sclerosis Function and ^{31}P MRS Outcomes

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Abstract

PURPOSE: We determined if a high-intensity aerobic exercise program would be safe, improve expected fitness and clinical outcomes, and alter exploratory phosphorous magnetic resonance spectroscopy (^{31}P MRS) outcomes in persons with multiple sclerosis (PwMS).

METHODS: This open-label prospective pilot study compared 2 cohorts of ambulatory PwMS matched for age, sex and VO_2max . Cohorts underwent 8-weeks of high-intensity aerobic exercise (MS-Ex, n=10) or guided stretching (MS-Ctr, n=7). Aerobic exercise consisted of four 30-minute sessions per week while maintaining 70% maximal heart rate. Changes in cardiorespiratory fitness, clinical outcomes, and ^{31}P MRS of tibialis anterior muscle (TA) and brain were compared. Cross-sectional ^{31}P MRS comparisons were made between all MS participants and a separate matched healthy control (HC) population.

RESULTS: The MS-Ex cohort achieved target increases in VO_2max (mean +12.7%, $p < 0.001$, between-group improvement $p = 0.03$). One participant was withdrawn for exercise-induced syncope. The MS-Ex cohort had within-group improvements in fat mass (−5.8%, $p = 0.04$), lean muscle mass (+2.6%, $p = 0.02$), Symbol Digit Modalities Test (+15.1%, $p = 0.04$), and cognitive subscore of the Modified Fatigue Impact Scale (MFIS: −26%, $p = 0.03$) while only the physical subscore of the MFIS improved in MS-Ctr (−16.1%, $p = 0.007$). ^{31}P MRS revealed significant within-group increases in MS-Ex participants in TA rate-constant of PCr recovery (k_{PCr} ; +31.5%, $p = 0.03$) and ATP/PCr (+3.2%, $p = 0.01$), and near significant between-group increases in TA k_{PCr} ($p = 0.05$) but no significant changes in brain ^{31}P MRS following exercise. Cross-sectional differences existed between MS and HC brain PCr/Pi (4.61 ± 0.44 , 3.93 ± 0.19 $p = 0.0019$).

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Supplemental Digital Content

Table: Changes in deep gray matter volumes following aerobic exercise among the MS-Exercise cohort

CONCLUSION: High-intensity aerobic exercise in PwMS improved expected cardiorespiratory and clinical outcomes but provoked one serious adverse event. ³¹P MRS may serve to explore underlying mechanisms by which aerobic exercise exerts cerebral benefits.

Keywords

Multiple sclerosis; phosphorus MR spectroscopy; Aerobic exercise; Cognition; Clinical trial

INTRODUCTION

The benefits of exercise in the general population are well known, and exercise interventions to improve general fitness and reduce symptoms in multiple sclerosis (MS) are becoming mainstream (1). Fewer trials have examined the safety, tolerability, and impacts of high-intensity aerobic exercise for people with MS (PwMS), or explored the cerebral mechanisms underlying the clinical improvements.

While PwMS are reported to have lower baseline fitness, they generally respond as expected to aerobic exercise interventions (2, 3). These aerobic exercise programs are typically of moderate intensity defined using the *American College of Sport Medicine's Guidelines for Exercise Testing and Prescription* as 50–70% VO₂max as opposed to high intensity (>70%) (4). The most frequently reported clinical benefits of aerobic exercise in MS are improving fatigue, cognition and mobility, all of which are common, disabling, and stubbornly treatment-resistant symptoms in MS (5).

The cerebral benefits of aerobic exercise are well-established. In rodents, physical activity increases levels of brain-derived neurotrophic factor (BDNF) and growth factors associated with improved cognition, and both preventing demyelination and promoting hippocampal neurogenesis and synaptic plasticity (6). Healthy adults show increased hippocampal volumes accompanied by improvements in memory following a 12 month aerobic exercise intervention compared to stretching (7). These changes may be associated with improved cerebral perfusion and IGF-1 levels (8). Exercise also delays onset and slows progression of cognitive impairment and brain atrophy in older adults without neurologic disease (9).

The symptomatic and neuroanatomic benefits of physical activity in MS are also evident. Cross-sectional studies in MS reveal positive associations between levels of physical activity and walking performance with fatigue, cognitive processing speed, brain volumes, and tract integrity (10–12). Longitudinal studies of aerobic exercise generally, although not invariably, demonstrate improvements in fitness and MS symptoms (3, 13, 14). The variations in results may be due to differences between studies in choice of exercise modality, duration, intensity, comparator group activity and outcome measures. Changes in peripheral cytokines, BDNF, and immunological factors have also been variably noted in response to aerobic exercise in MS and other populations (8, 15, 16).

What are the underlying mechanisms by which aerobic exercise improves brain functional outcomes and increases volumes and tract integrity? One hypothesis is that the improved mitochondrial function in skeletal muscle resulting from aerobic exercise could also occur in the brain. Improved mitochondrial function, in turn, would reduce oxidative damage, prevent

apoptosis, and have restorative properties leading to improved functional outcomes (17). Skeletal muscle mitochondrial function can be demonstrated using phosphorous MR spectroscopy (^{31}P MRS). This technique is primarily used to measure the resynthesis of phosphocreatine (PCr) following exercise as a measure of the oxidative capacity of skeletal muscle as well as demonstrating the 3 adenosine triphosphate (ATP), phosphocreatine (PCr), and inorganic phosphate (Pi) peaks (18). The resynthesis of PCr, measured as a rate constant of recovery (k_{PCr}), was shown to be lower in dorsiflexor muscles of PwMS than controls immediately following exercise (19). Increased k_{PCr} indicates the improved ability of muscle to restore PCr/ATP ratios depleted by exercise suggesting improved mitochondrial function (18). The introduction of high field (7 tesla) MRI has now improved the signal to noise ratio allowing a similar evaluation of energy peaks, although not k_{PCr} , in the brain (20). To our knowledge, these outcomes have not been explored as a potential marker of mitochondrial function in relation to an aerobic exercise protocol.

In this pilot study, we hypothesized that compared to a stretching control, a short duration, high-intensity exercise program would be well tolerated and would improve the expected outcomes of cardiorespiratory fitness, body composition, and MS symptoms of cognitive dysfunction and fatigue in PwMS. As an exploratory outcome, we hypothesized that ^{31}P MRS would detect altered ratios of ATP, PCr, and Pi in the brain mirroring the expected changes in the of the tibialis anterior muscle (TA) in response to the exercise intervention.

MATERIALS AND METHODS

Study Design:

The unblinded prospective pilot cohort study (NCT02263339) protocol was approved by the Institutional Review Board at Oregon Health & Science University (OHSU). Written informed consent was obtained from study participants prior to enrollment.

Participants:

PwMS were recruited on a convenience basis from the OHSU MS Clinic and local community. Inclusion criteria were ages 18–65 years, diagnosis of relapsing remitting MS (2010 McDonald criteria), and fully ambulatory (Expanded Disability Status Scale, EDSS, 4.0) (21). Exclusion criteria were MS exacerbation or the use of intravenous corticosteroids or antibiotics within 30 days of screening, contraindications to MRI, or uncontrolled cardiopulmonary disease. There were no specific criteria for fatigue or cognition at baseline. MS-Exercise (MS-Ex) participants were recruited first, followed by MS-Control (MS-Ctr). Cohorts were matched for sex, age ± 10 years, and baseline aerobic fitness (incremental maximal exercise test, $\text{VO}_{2\text{max}}$) $\pm 10\%$. A third cohort of healthy controls (HC) matched to the MS-Ex cohort for sex, age ± 10 years, and baseline $\text{VO}_{2\text{max}}$ test $\pm 10\%$ was recruited for cross-sectional comparison of ^{31}P MRS outcomes.

Study Interventions:

The aerobic exercise intervention consisted of 4 sessions per week of aerobic exercise for 30 minutes maintained at a target heart rate for 8 consecutive weeks. Exercise training target heart rate was at least 70% of measured maximal heart rate for each subject. This target

heart rate was determined by the heart rate during exercise testing when the RER (respiratory exchange ratio) was between 0.9 and 0.99 which is just below the anaerobic threshold. This allowed subjects to aerobically exercise train without being anaerobic. Aerobic exercise sessions were directly supervised by an exercise physiologist at the OHSU Human Performance Laboratory (HPL). Participants exercised on a treadmill (n=9) or cycle ergometer (n=1) chosen by the physiologist based on individual abilities. The study goal was a 5–15% increase in VO_2max per expert opinion (KK) given expectations for a population with a chronic disease. The control intervention was a guided static stretching program for 30 minutes per day, 4 days per week, for 8 weeks. Initial training and a paper guide to the stretches was provided by an exercise physiologist at the HPL, followed by HPL visits every 2 weeks for the same exercise physiologist to review stretching logs and encourage adherence to the program. All study participants were instructed to avoid any other change to baseline activity levels or dietary habits for the duration of the study. Reports of adverse events were collected during study visits and reviewed descriptively, and compliance with study visits tabulated.

Study Outcomes

Cardiorespiratory fitness testing: All participants underwent measurements of resting systolic blood pressure (SBP) and heart rate (HR). After pulmonary function tests, participants completed a physician-supervised, electrocardiogram-monitored VO_2max test with measurement of maximal oxygen uptake in accordance with the published guidelines (22). A maximal test was defined as one in which the participant reached a plateau in oxygen uptake, a respiratory exchange ratio (RER) above 1.1, or in which the participant stopped despite urging by the testing staff. Aerobic capacity outcomes of interest were VO_2max (ml/kg/min), maximum work (W) and total exercise time.

Body composition testing: Participants had weight, body mass index (BMI), body fat percentage by bioelectrical impedance (Tanita BC-558 bioelectrical impedance analyzer), fat mass and lean mass tested at baseline and following the 8 week intervention.

Phosphorus Magnetic Resonance Spectroscopy (^{31}P MRS): A Siemens 7T Magnetom system (Erlangen, Germany) was used to collect ^{31}P MRS data prior to and following the study interventions. The ^{31}P MRS TA muscle protocol used a dual-tuned $^{31}\text{P}/^1\text{H}$ surface coil (4 cm x 9.5 cm oval, with longer axis aligned to the muscle length) positioned over the center of the TA muscle of the right leg. Right legs were positioned in a home-built exercise device consisting of a Plexiglas foot pedal and adjustable rubber band that isolated dorsiflexion of the ankle against a fixed load. ^{31}P MRS protocol of the TA muscle consisted of a 2–3 minute period of baseline rest, a three minute exercise period estimated to deplete phosphocreatine (PCr) by 20–40%, and a 4–10 minute recovery period during which no exercise was performed. The exercise consisted of a foot-flexion exercise synchronized to a metronome set to 40 beats/min ^{31}P spectra were acquired continuously at 1.2 s intervals throughout. For brain, high resolution MPRAGE anatomic (0.8 mm isotropic) images were acquired for tissue segmentation in a sagittal orientation (23). A 3D brain ^{31}P MRS was performed using a ^{31}P head coil with a ^1H Halo coil setup (23). Low-resolution phosphorus B_1 maps were acquired for RF coil inhomogeneity correction.

The primary ^{31}P MRS TA outcome of interest was the rate-constant of PCr recovery (k_{PCr}) following a bout of mild exercise. Additionally ratios of PCr and total ATP to inorganic phosphate (P_i) and ratio of total ATP to PCr were captured for both TA and brain. Gamma-ATP ($\gamma\text{-ATP}$) was used as the marker of total ATP in this study.

Clinical outcomes: The Symbol Digit Modalities Test (SDMT), a measure of mental processing speed, was the cognitive measure (24). The patient-reported Modified Fatigue Impact Scale (MFIS), validated for use in MS, assessed fatigue (25). The total score consists of physical, cognitive and psychosocial sub-scores. The Timed Up-and-Go (TUG) test consisting of rising from a chair, walking 7 meters, turning, and returning to the chair measured timed mobility, and the six-minute walk test (6MWT) measured walking endurance (26, 27).

Statistical Analysis—Statistical analysis was performed using Stata 13.1 (28). Baseline demographics (Table 1) were analyzed using independent two sample t-tests (continuous variables), Fisher Exact tests (categorical variables) and Mann-Whitney U test (ordinal variables). To determine whether there is any difference between pre-score and post-score within each group (Tables 2, 3 & 4), paired t-tests were used. Pre-post change score was calculated by subtracting pre-score from post-score (post minus pre). Between-group change p-value shows if change score (post minus pre score) differs between MS-Ex and MS-Control groups and was calculated using independent two sample t-tests.

RESULTS

The study was conducted between November, 2014, and April, 2016. Eighteen MS participants consented and started the study. One MS-Ex participant was withdrawn from the study after a near-syncopal event at one visit and a syncopal event following completion of the exercise session on another visit prompting a visit to the emergency department. The participant, whose data was not included in analysis, had a childhood history of exercise-induced syncope thought to have been outgrown. There were no other adverse events. Compliance with study visits was 99.4%. At baseline, 8 of the 10 MS-Ex achieved a Max RER 1.1 or greater while all MS-Ctr and HC participants met this target. At exit, only 1 MS-Ex participant did not meet RER 1.1. When RER wasn't met, the VO_2max test was terminated by the participant. MS-Ex and MS-Ctr cohorts did not differ significantly in matching characteristics of age, sex, VO_2max (Table 1). The HC cohort compared for baseline ^{31}P MRS outcomes were younger (36.0 ± 7.5 , 46.3 ± 8.9 years, $p=0.01$) than the MS participants (Table 5).

Changes in cardiorespiratory fitness and body composition (Table 2)

Nine of 10 MS-Ex achieved the study goal of 5–15% increase in VO_2max , with mean increase of 12.7% ($p<0.001$) vs none of the MS-Ctr achieving this goal (mean increase 1.1%, $p=0.82$, between group difference $p=0.03$). Eight out of 10 MS-Ex achieved 10% increase in VO_2max , considered clinically meaningful (3). Maximum work and total exercise time also improved in the MS-Ex cohort with significant within- and between-group changes. Neither intervention group demonstrated significant changes in HR or blood

pressure parameters. For body composition, percent body fat and lean muscle mass improved within the MS-Ex cohort only (-5.8% , $p=0.04$, and $+2.6\%$, $p=0.02$, respectively), although neither reached a statistically significant improvement over the MS-Ctr cohort.

Changes in clinical outcomes of cognition, fatigue, and walking performance (Table 3)

The MS-Ex cohort demonstrated statistically significant improvements in mean SDMT score from baseline (mean $+7$ points, $+15.1\%$, $p=0.04$) while MS-Ctr did not (mean $+1$, $+1.9\%$, $p=0.59$, between-group $p=0.13$). Similarly, the cognitive fatigue subscore of the MFIS improved significantly in the MS-Ex cohort from baseline (-26% , $p=0.03$) but without a significant between group difference. Neither cohort exhibited significant changes in the TUG or 6MTW.

Changes in ^{31}P MRS of the right TA and brain (Table 4)

In the right TA muscle, the MS-Ex cohort demonstrated a significant within-group increase in the k_{PCr} ($+31.5\%$, $p=0.03$) and ATP/PCr ratio ($+3.2\%$, $p=0.01$). The change in k_{PCr} was nearly but not significantly improved over the MS-Ctr cohort ($p=0.05$). No significant changes were seen in ^{31}P MRS outcomes in the brain following interventions for either cohort.

Cross-sectional comparison of ^{31}P MRS outcomes between matched MS and HC cohorts (Table 5)

Differences in baseline ratios of brain markers of high-energy phosphates were found between the MS and HC participants. These included a greater cerebral PCr/Pi (MS 4.61 ± 0.44 , HC 3.93 ± 0.19 , $p=0.002$) and lower ATP/PCr (MS 1.01 ± 0.05 vs. HC 1.08 ± 0.06 , $p=0.001$) among the MS cohort. The TA muscle ATP/PCr ratio was significantly lower in the MS participants than HC cohort (0.29 ± 0.01 vs. 0.30 ± 0.01 , $p=0.02$). Additional variables in Table 5 include the matching characteristics between cohorts and baseline differences in functional study outcomes.

DISCUSSION

In this 8 week study, PwMS completing a high-intensity aerobic exercise program demonstrated improvements in cardiorespiratory function, body composition, mental processing speed (SDMT), and cognitive fatigue (MFIS) compared to PwMS doing a stretching program. Overall the aerobic exercise program was well tolerated, however the occurrence of exercise-induced near syncope in one MS-Ex subject suggests caution when initiating similar programs. Important to the study design was the matched control group stretching program of equal frequency and duration along with professional support from study staff rather than a wait list control. Improvement in TA ^{31}P MRS outcomes supported the VO₂max changes found on cardiorespiratory testing. While cerebral ^{31}P MRS did not change following the aerobic exercise intervention, cross-sectional differences these markers of brain energy production between MS and matched healthy controls may point to the as yet unknown underlying mechanisms by which aerobic exercise exerts its cognitive benefits.

While there are now several well-designed studies demonstrating the safety and efficacy of high-intensity aerobic exercise in MS populations, at the time the present study was conceived, this was less clear (3) (29, 30). Historically, PwMS were advised to avoid exercise for fear of worsening their disease, in part from overheating. The present study supports that even relatively sedentary PwMS can benefit rapidly from aerobic exercise. The re-emergence of exercise-induced syncope in one study participant reminds us that graded intensity and/or direct supervision may be warranted in persons not accustomed to high intensity exercise. Questions addressed in newer studies include evaluating combinations of aerobic and resistance training as well as developing exercise programs for non-ambulatory PwMS to further inform clinical guidelines.

The MS-Ex participants in our study demonstrated impressive increases in VO_{2max} , with 90% achieving the study goal of 5%, and 80% achieving what is now considered a clinically meaningful 10% improvement by study end (3). At the same time, the aerobic exercise participants increased their SDMT score by 6 points more than the MS-Ctr group, an increase that can be considered clinically meaningful (31). The improvements parallel SDMT changes found in other high-intensity aerobic exercise studies with similar VO_{2max} gains (32). The MFIS is also utilized in aerobic exercise studies and appears sensitive to exercise interventions (13, 32). While not all studies find improvements in cognitive tests and fatigue self-ratings, subgroup analyses sometimes reveal that the most impaired are most likely to demonstrate a benefit, suggesting a ceiling effect of the tests (33). Our study did not select for baseline cognitive impairment or fatigue, however our comparison with HC demonstrated baseline cross-sectional differences (Table 5). Ceiling effects may have also played a role in the lack of improvement in the 6MWT and TUG walking tests, which have been shown to improve following an exercise intervention in an MS population with a higher level of baseline disability, although baseline 6MTW results was also lower in the MS than HC participants (13). As a pilot study, sample size was not powered on these clinical outcomes which might require larger numbers, longer studies, and possibly measures not thought *a priori* to change after such a brief intervention such as patient-reported psychosocial and participation outcomes (34). Overall, the clinical benefits achieved in this study were as expected based on current literature.

The mechanisms by which aerobic exercise improves cognitive function are debated and are likely many. In a recent review, El-Sayes *et al* proposes a model for neuroplasticity following acute and chronic effects of aerobic exercise starting from molecular and cellular changes, and leading to structural/functional, and finally behavioral changes (35). This more general model of neuroplasticity appears to hold true for MS as aerobic exercise favorably changes levels of neurotrophins, neurotransmitters, inflammatory factors, hormones, neuromodulators, and more which are also associated with improved cognition, although these findings are neither specific to MS populations, nor are they detected in every study (12, 15, 36). While presented sequentially, these structural and behavioral changes can occur early as evidenced by neurogenesis detected in exercising rodents within days, verbal memory and serum matrix metalloproteinases after 3 weeks in MS, and increased hippocampal volume and resting-state functional connectivity after 3 months (35, 37, 38). Our own brain MRI segmentation results on participants in this study did not demonstrate consistent volumetric changes in hippocampal, thalamic, or other brain substructures (see

Table, Supplemental Digital Content 1, Changes in deep gray matter volumes following aerobic exercise among the MS-Exercise cohort). Longer-term exercise studies do more consistently demonstrate growth of brain substructures correlating with cognitive improvement (7, 39).

Demonstration of improved bioenergetic function after aerobic exercise in the TA muscle using ^{31}P MRS raises the possibility that aerobic exercise also improves mitochondrial function in the brain. Increased oxygen consumption and glucose metabolism might, in turn, drive the molecular and cellular processes leading to neuroplasticity and improved cognition. We found cross-sectional differences in ATP metabolites between MS and HC populations, similar to Kuvshinov et al., although they expressed the peaks as percentages rather than ratios (20). Unclear is if the lack of change in metabolite ratios in the MS-Ex cohort following aerobic exercise was a sample size, effect size, or study duration issue, or a true finding. However the baseline differences encourage further exploration into this potential biomarker by addressing these study design issues.

The study was limited by the small sample size and restricted permitted disability among MS participants which were due to the pilot nature of the study. Other limitations stemmed from the study design including the brevity of cognitive and fatigue testing. The SDMT is measure of mental processing speed and not specific to the cognitive deficits such as learning and memory known to commonly occur in MS. Validated MS batteries of cognitive tests exist that might have greater sensitivity to demonstrate efficacy of the interventions (40). Yet newer evidence suggests that mental processing speed may be the cognitive domain best associated with aerobic capacity and best stand-alone cognitive task for MS (14, 31). Other study limitations include lack of confounder assessments such as mood and sleep. Finally, the lack of randomized assignment to intervention cohorts tempers the robustness of the conclusions.

CONCLUSIONS

In conclusion, a brief, high-intensity, aerobic exercise intervention compared to stretching resulted in expected improved fitness, body composition, and clinically significant increases in cognitive performance and cognitive fatigue in PwMS. The adverse event suggests caution when starting high-intensity aerobic exercise in PwMS. The cross-sectional differences in cerebral ^{31}P MRS encourage further exploration of this potential biomarker of the bioenergetic contributions to neuroplasticity in response to aerobic exercise.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Baseline demographics and matching characteristics between MS-Exercise (MS-Ex) and MS-Control (MS-Ctr) cohorts. All values are mean $\pm$ SD unless otherwise indicated.

Variable		MS-Ex (n= 10)	MS-Ctr (n=7)	p-value
Matching characteristics	Age (years)	44.7 $\pm$ 9.4	48.7 $\pm$ 8.4	0.38
	Females (%)	90%	86%	1.00
	VO ₂ max (mL/min/Kg)	30.0 $\pm$ 9.3	29.0 $\pm$ 7.8	0.82
MS duration (years)		14.6 $\pm$ 6.5	20.2 $\pm$ 10.4	0.19
EDSS (Median, Range)		3.5 (2.5–4)	3 (2–4)	0.19
Systolic BP (mmHg)		113.9 $\pm$ 9.6	113.4 $\pm$ 7.3	0.90
Heart rate (bpm)		65.6 $\pm$ 11.8	67.4 $\pm$ 8.2	0.59
BMI (Kg/m ²)		26.9 $\pm$ 4.4	29.6 $\pm$ 7.1	0.34
Body fat by BIA (%)		32.9 $\pm$ 11.9	23.3 $\pm$ 7.1	0.09
³¹ P MRS_TA	k _{PCr} (s ⁻¹)	0.022 $\pm$ 0.005	0.024 $\pm$ 0.010	0.64
	PCr/P _i	6.36 $\pm$ 0.61	6.642 $\pm$ 0.910	0.50
	ATP/P _i	0.92 $\pm$ 0.10	0.92 $\pm$ 0.149	0.98
	ATP/PCr	0.29 $\pm$ 0.01	0.279 $\pm$ 0.020	0.16
³¹ P MRS_Brain	PCr/P _i	4.61 $\pm$ 0.44	4.34 $\pm$ 0.27	0.84
	ATP/P _i	4.61 $\pm$ 0.49	4.14 $\pm$ 0.38	0.14
	ATP/PCr	1.01 $\pm$ 0.056	0.96 $\pm$ 0.05	0.05

ATP, adenosine triphosphate; BIA, bioelectrical impedance analysis; BMI, body mass index; BP, blood pressure; bpm, beats per minute; EDSS, Expanded Disability Status Scale; Kg, kilograms; k_{PCr}, phosphocreatine recovery rate constant; m², square meters; min, minute; mL, milliliters; MS, multiple sclerosis; ³¹P MRS; ³¹P magnetic resonance spectroscopy; TA, tibialis anterior muscle; PCr, phosphocreatine; P_i, inorganic phosphate; s, seconds.

Table 2.

Changes in cardiorespiratory fitness and body composition following interventions between MS-Exercise (MS-Ex) and MS-Control (MS-Ctr) cohorts.

Variable	MS-Ex (n=10)				MS-Ctr (n=7)			
	Pre	Post	Pre-post change (%), <i>p</i> -value		Pre	Post	Pre-post change (%), <i>p</i> -value	Between-group change <i>p</i> -value
VO ₂ max (mL/kg/min)	30.0 ± 9.3	33.8 ± 8.5	+12.7, <0.001		29.0 ± 7.8	29.3 ± 6.4	+1.1, 0.82	0.03
Maximum work (W)	167.7 ± 52.8	216.6 ± 57.8	+29.1, <0.001		185.3 ± 40.7	184.6 ± 43.5	-0.53, 0.69	<0.001
Total exercise time (min)	11.5 ± 2.9	13.8 ± 3.8	+20.5, 0.002		11.9 ± 2.2	11.8 ± 1.7	-0.8, 0.72	0.004
Systolic BP (mmHg)	113.9 ± 9.6	109.7 ± 9.8	-3.74, 0.31		113.4 ± 7.3	109.8 ± 7.5	-3.14, 0.09	0.89
Resting heart rate (bpm)	65.6 ± 11.8	67.4 ± 8.2	+2.74, 0.59		67.4 ± 11.2	66.1 ± 11.2	-1.91, 0.52	0.47
Body fat by BIA (%)	32.9 ± 11.9	31.0 ± 11.0	-5.8, 0.04		23.3 ± 7.1	23.7 ± 8.1	+4.3, 0.56	0.06
Lean muscle mass (kg)	46.6 ± 7.0	47.8 ± 6.8	+2.6, 0.02		61.8 ± 9.7	61.4 ± 11.1	-0.56%, 0.71	0.10

BIA, bioelectrical impedance analysis; BP, blood pressure; bpm, beats per minute; HC-Ex, healthy control aerobic exercise cohort; kg, kilograms; mL, milliliters; min, minute; mmHg, millimeters of mercury; MS, multiple sclerosis; MS-Ctr, MS stretching cohort; MS-Ex, MS aerobic exercise cohort. W, watts.

Table 3.

Changes in clinical outcomes of a cognitive test (SDMT), fatigue rating scale (MFIS) and walking performance testes (6MTW and TUG) following interventions between MS-Exercise (MS-Ex) and MS-Control (MS-Ctr) cohorts.

Variable	MS-Ex (n=10)				MS-Ctr (n=7)			
	Pre	Post	Pre-post change (%), <i>p</i> -value		Pre	Post	Pre-post change (%), <i>p</i> -value	Between-group change <i>p</i> -value
SDMT total score	46.5 ± 13.4	53.5 ± 10.3	+15.1, 0.04		52 ± 6.9	53 ± 5.9	+1.9, 0.59	0.13
MFIS total score	31.3 ± 18.8	23.6 ± 17.3	-24.6, <i>0.05</i>		33.1 ± 16.4	28.8 ± 14.9	-12.9, 0.08	0.051
physical subscore	13.5 ± 6.7	10.6 ± 6.9	-21.5, 0.19		16.8 ± 7.9	14.1 ± 6.5	-16.1, 0.007	0.94
cognitive subscore	14.6 ± 11.2	10.8 ± 9.9	-26.0, 0.03		14.4 ± 7.7	12.6 ± 7.8	-12.9, 0.24	0.38
psychosocial score	3.2 ± 2.3	2.2 ± 2.1	-31.2, <i>0.05</i>		1.8 ± 1.5	2.1 ± 1.1	+15.4, 0.52	0.06
6MWT Distance (m)	429.1 ± 71.2	441.6 ± 58.2	+2.9, 0.47		503.5 ± 90.7	506.7 ± 96.9	+0.6, 0.82	0.69
TUG time (s)	15.1 ± 4.3	12.9 ± 3.2	-14.4, 0.11		12.7 ± 2.5	12.2 ± 2.1	-3.9, 0.17	0.28

6MWT, Six Minute Walk Test; m, meters; MFIS, Modified Fatigue Impact Scale; MS-Con, s, seconds; SDMT, Symbol Digit Modalities Test; TUG, Timed Up and Go.

Changes in ^3P Magnetic Resonance Spectroscopy of the right tibialis anterior muscle (TA) and brain following interventions between MS-Exercise (MS-Ex) and MS-Control (MS-Ctr) cohorts.

Table 4.

		MS-Ex (n=10)				MS-Ctr (n=7)				
	Variable	Pre	Post	Pre-post change (%), <i>p</i> -value		Pre	Post	Pre-post change (%), <i>p</i> -value		Between-group change <i>p</i> -value
TA	k _{PCr} (s ⁻¹)	0.022 ± 0.05	0.028 ± 0.01	+31.5, 0.03		0.024 ± 0.09	0.023 ± 0.008	-3.6, 0.69		0.05
	PCr/P _i	6.37 ± 0.61	6.32 ± 0.58	-0.8, 0.79		6.64 ± 0.91	6.28 ± 0.52	-5.5, 0.34		0.41
	ATP/P _i	0.93 ± 0.10	0.95 ± 0.08	+2.2, 0.47		0.93 ± 0.15	0.95 ± 0.09	+2.8, 0.69		0.92
	ATP/PCr	0.29 ± 0.01	0.30 ± 0.02	+3.2, 0.01		0.27 ± 0.02	0.30 ± 0.02	+9.1, 0.09		0.17
Brain	PCr/P _i	4.61 ± 0.44	4.78 ± 0.77	+3.75, 0.45		4.34 ± 0.26	4.79 ± 0.62	+10.5, 0.10		0.39
	ATP/P _i	4.61 ± 0.49	4.77 ± 0.75	+3.45, 0.49		4.13 ± 0.38	4.71 ± 0.64	+13.8, 0.08		0.26
	ATP/PCr	1.01 ± 0.056	1.00 ± 0.051	-0.96, 0.61		0.95± 0.04	0.98 ± 0.06	+2.9, 0.49		0.41

ATP, adenosine triphosphate; kPCr, phosphocreatine recovery rate constant; MS, multiple sclerosis; PCr, phosphocreatine; P_i , inorganic phosphate; s, seconds.

Table 5.

Cross sectional comparison between MS participants and a matched Healthy Control (HC) cohort. All values are mean $\pm$ SD unless otherwise indicated.

Variable		MS (N= 17)	Healthy Controls (N=7)	p-value
Matching characteristics	Age (years)	46.35 $\pm$ 8.95	36.0 $\pm$ 7.46	0.01
	Females (%)	88%	86%	0.86
	VO ₂ max (mL/min/Kg)	29.61 $\pm$ 8.51	34.1 $\pm$ 5.43	0.21
SDMT total score		48.76 $\pm$ 11.27	62.57 $\pm$ 10.84	0.01
MFIS Total score		32.05 $\pm$ 17.35	13.14 $\pm$ 9.42	0.01
6MWT Distance (m)		459.75 $\pm$ 85.83	567.14 $\pm$ 85.82	0.01
TUG time (s)		14.10 $\pm$ 3.78	12.54 $\pm$ 1.89	0.31
³¹ P MRS TA	k _{PCr} (s ⁻¹)	0.022 $\pm$ 0.007	0.028 $\pm$ 0.01	0.16
	ATP/Pi	0.92 $\pm$ 0.11	0.95 $\pm$ 0.06	0.49
	PCr/Pi	6.48 $\pm$ 0.74	6.33 $\pm$ 0.51	0.62
	ATP/PCr	0.29 $\pm$ 0.01	0.30 $\pm$ 0.01	0.02
³¹ P MRS Brain	ATP/P _i	4.41 $\pm$ 0.50	4.25 $\pm$ 0.35	0.42
	PCr/P _i	4.49 $\pm$ 0.39	3.93 $\pm$ 0.19	0.002
	ATP/PCr	0.98 $\pm$ 0.05	1.08 $\pm$ 0.06	0.001

ATP, adenosine triphosphate; BIA, bioelectrical impedance analysis; BMI, body mass index; BP, blood pressure; bpm, beats per minute; Kg, kilograms; k_{PCr}, phosphocreatine recovery rate constant; m, meters; min, minute; mL, milliliters; MFIS, Modified Fatigue Impact Scale MS, multiple sclerosis; ³¹P MRS; 31 phosphorous magnetic resonance spectroscopy; PCr, phosphocreatine; P_i, inorganic phosphate; 6MWT, Six Minute Walk Test; SDMT, Symbol Digit Modalities Test; TA, tibialis anterior muscle; TUG, Timed Up and Go test