Effects of High-Intensity Resistance Training on Strength, Mobility, Balance, and Fatigue in Individuals With Multiple Sclerosis: A Randomized Controlled Trial

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Background and Purpose: Resistance exercise via negative, eccentrically induced work (RENEW) has been shown to be associated with improvements in strength, mobility, and balance in multiple clinical populations. However, RENEW has not been reported for individuals with multiple sclerosis (MS).

Methods: Nineteen individuals with MS (8 men, 11 women; age mean = 49 ± 11 years; Expanded Disability Status Scale [EDSS] mean = 5.2 ± 0.9) were randomized into either standard exercise (STAND) or standard exercise and RENEW training (RENEW) for 3 ×/week for 12 weeks. Outcome measures were lower extremity strength (hip/knee flexion and extension, ankle plantar and dorsiflexion, and the sum of these individual values [sum strength]); Timed Up and Go (TUG), 10-m walk, self-selected pace (TMWSS) and maximal-pace (TMWMP), stair ascent (S-A) and descent (S-D) and 6-Minute Walk Test (6MWT), Berg Balance Scale (BBS), Fatigue Severity Scale (FSS).

Results: No significant time effects or interactions were observed for strength, TUG, TMWSS, TMWMP, or 6MWT. However, the mean difference in sum strength in the RENEW group was 38.60 (representing a 15% increase) compared to the sum strength observed in the STAND group with a mean difference of 5.58 (a 2% increase). A significant interaction was observed for S-A, S-D, and BBS as the STAND group improved whereas the RENEW group did not improve in these measures.

Discussion and Conclusions: Contrary to results in other populations, the addition of eccentric training to standard exercises did not result in significantly greater lower extremity strength gains in this group of individuals with MS. Further, this training was not as effective as standard exercise alone in improving balance or the ability to ascend and descend stairs. Following data collection, reassessment of required sample size indicates we were likely underpowered to detect strength differences between groups.

Key words: balance, eccentric ergometry, fatigue, mobility, multiple sclerosis, resistance training, strength

Background AND Purpose

Multiple sclerosis (MS) is a degenerative disease of the central nervous system. Individuals with MS often report symptoms of fatigue and muscle weakness, and are often less physically active than age-matched adults. As a result, a downward spiral of function often occurs resulting in difficulties in mobility, balance, and an increased risk of falling.

Regular exercise has been shown to improve or maintain muscle strength, and to improve mobility and balance in elderly individuals as well as those with neurological disabilities. Historically, exercise was avoided in individuals with MS, because of the apparent increase of difficulty with mobility, weakness, and fatigue following exercise. However, over the past decade the benefits of exercise have been demonstrated in individuals with MS. Traditional exercise prescriptions for individuals with MS mimic those for the general population and includes primarily aerobic and endurance exercise, and secondarily strengthening and flexibility training. Aerobic training results in increases in peak oxygen uptake, increased muscle strength and endurance, with equivocal results reported for changes in activity level, balance, and gait pattern in individuals with MS.

The primary focus of exercise for patients with MS over the past decade has been on aerobic exercise; however, recently there has been interest in resistance exercise training. Resistance training studies for individuals with MS have reported improvements in leg strength, decreased perception of fatigue, and an increase in muscle power; however, the results for balance, gait pattern, and functional capacity are mixed. These latter mixed results are contrary to results in other populations, including older adults and persons with other neuromuscular diseases wherein it appears that resistance training improves muscle strength with concomitant improvements in mobility, balance, and overall function.

Resistance training studies in individuals with MS have been of low intensity, typically using a progressive resistance exercise regimen of 60% and 80% of a maximal
voluntary contraction.\textsuperscript{18,31} Other studies have focused on home programs using Theraband\textsuperscript{32} or a weighted (0.5\%-1.5\% of body weight) vest for resistance.\textsuperscript{16} It is possible that improvements in functional gains may not be evident without a sufficient stimulus to induce a strength change. High intensity eccentric resistance training produces high-muscle forces at a low-metabolic cost or low-perceived exertion.\textsuperscript{33} This training has been shown to provide a potent stimulus for muscle hypertrophy and strength,\textsuperscript{34,35} and appears to be a more effective stimulus for muscle hypertrophy and strength compared to concentric training.\textsuperscript{36}

Resistance exercise via negative, eccentrically induced work (RENEW) has recently been shown to be safe and feasible for multiple populations, including healthy elderly individuals,\textsuperscript{37} frail elders,\textsuperscript{38} individuals with Parkinson disease,\textsuperscript{39,40} and cancer survivors.\textsuperscript{31,42} Additionally, high-intensity resistance training has resulted in gains in mobility and balance for individuals with neurological disorders,\textsuperscript{40,43–45} those with muscle weakness,\textsuperscript{38,46,47} and those having difficulty tolerating aerobic exercise.\textsuperscript{31,48–51} The use of eccentric ergometric resistance training for individuals with MS is appealing, as RENEW may be the stimulus needed for improving both strength and function that low-intensity resistance strength training has not provided previously. The effects of a high-intensity RENEW exercise program has not been reported in the literature for individuals with MS.

The purpose of this study was to assess the effects of a program of high-intensity RENEW exercise combined with standard exercises on lower extremity strength, mobility, balance, and fatigue in individuals with MS compared to a standard exercise program over 12 weeks. We compared 2 groups of individuals with MS, one group received standard exercises (STAND group) and the other group received standard exercise and high-intensity RENEW exercise (RENEW group) using an eccentric ergometer. We hypothesized that after training the high-intensity RENEW exercise group would demonstrate greater improvements in muscle strength and therefore mobility and balance compared to the STAND group.

**METHODS**

**Study Design**

A prospective, longitudinal, randomized intervention trial was performed. The STAND and RENEW groups participated in a pre-post clinical design with a 12-week training program. An a priori power analyses for a $2 \times 2$ ANOVA was performed for the main effects of time (pre and post) and training type (STAND and RENEW) with an $\alpha$ level set at .05 for each test and a desired power level set at .80. Our previous studies with this RENEW paradigm have yielded time effect size estimates (between baseline and posttest) equal to 3 SDs or more. To be more conservative, we estimated that time effect size in the RENEW group would be equal to at least 2.0 SDs. We estimated that change from baseline to 12 weeks in the STAND group would be equal to 1.0 SD. In this conservative scenario, the calculated sample size was 7 for each group. Twenty participants were to be recruited with 30\% attrition expected so that 14 individuals (7 in each group) would be able to complete the study.

**Participants**

Male and female adults with MS from within the University of Utah and VA physicians, Utah State Chapter of National Multiple Sclerosis Society and local support groups were recruited throughout the greater Salt Lake City, Utah region from July 2005 to June 2007. To be included, individuals had to have a diagnosis of definite MS established by a physician with no exacerbations in the past 3 months, be between the ages of 18 and 65 years, be ambulatory with or without an assistive device or braces, have impaired gait pattern (assessed by physical therapist), and have no lower extremity joint problems. They must not have been participating in a regular strength training exercise program defined as a minimum of 10 minutes, 2 times per week. The flow diagram of enrollment based on the Consolidated Standards of Reporting Trials (CONSORT) statement is illustrated in Figure 1.\textsuperscript{52} The purpose and procedures of the study were explained to the participants and a consent
Training Programs

The STAND group and the RENEW group both participated in standard exercises 3 times per week for 45 to 60 minutes per session for 12 weeks. The only difference between the groups was that the STAND group received no focused lower extremity resistance training, whereas high-intensity lower extremity eccentric ergometric resistance exercise was performed by the RENEW group. Standard exercises included aerobic training, lower extremity stretching, upper extremity strength training, and balance exercises. The aerobic training was performed on a seated recumbent stepper (NuStep Inc., Ann Arbor, Michigan); training sessions began at 3 minutes on the recumbent stepper, and workload and time was progressed as tolerated with a maximum of 15 minutes. Stretching of bilateral hamstrings, quadriceps, and triceps surae muscles was performed for 30 seconds initially and progressed to a maximum of 2 minutes for each muscle. Upper extremity resistance exercises (both machines and free weights, 10 repetitions to fatigue) were performed for biceps, triceps, rhomboids, and latissimus dorsi muscles while seated. Balance exercises included standing on a wobble board while maintaining balance as tolerated with a maximum of 15 minutes. Upper extremity stretching exercises were reviewed. Pedal cadence was set to 15 to 20 rpm. The participant applied resistance from 10° to 90° of knee flexion. Sessions began with orientating the participant to the timing of the machine by allowing the machine to passively move the legs through the range of motion. Participants progressed to 1 to 5 minute sessions on the stepper over the first 2 weeks, and then to a maximum of 14 minutes per session (average time maximum training was 10 minutes) over the next 12 weeks.

The progression of the eccentric exercise work rate was determined based on the rating of perceived exertion (RPE) as assessed using the 20-point Borg scale. The perceived exertion during exercise was initially limited to “very, very light” (7/20) for 5 minutes during the first week. During week 2 (sessions 4-6) the participant’s perceived exertion was progressed to “very light” (9/20). In week 3 training was increased to a “fairly light” (11/20) exertion level. In the last 8 weeks of training the perceived exertion was between “fairly light” and “somewhat hard” (13/20). Once the participant achieved a RPE of “somewhat hard” subjects were instructed to maintain that RPE throughout the exercise program duration. With these RPE contraints, the goal was to progressively increase the eccentric load to the leg muscles each session by increasing the total amount of negative work per session. Total work was defined as the accumulation of work performed as the participant applied a force to the pedal whereas the motor moved the pedal toward them. Time was added if needed to meet the goal of increasing the amount of total work achieved per session. Prior RENEW studies have documented that this slow progression of the resistance utilized in this study has not resulted in delayed onset muscle soreness, a typical concern of high-intensity eccentric ergometry.33 In the present study, this progression did not result in fatigue or increased muscle soreness. Fatigue, assessed pre- and posttraining, decreased over the 12 weeks from 4.2/10 to 3.1/10 on a visual analog scale. Muscle soreness did not exceed 1/10 prior to a session on training days.

Outcome Measures

All outcome measures were performed by the same physical therapist for strength (author EG) and balance and mobility (author HH) for pre- and postassessment. All measures were performed at the University of Utah Rehabilitation and Wellness Clinic. Strength, mobility, and balance measures were each performed on separate days with 48 hours between tests. Postassessment measures were performed 5 to 7 days after training to allow sufficient rest time.
Strength Assessment

Maximum voluntary isometric contractions of 5 lower extremity muscle groups were measured bilaterally using a fixed dynamometry system (QMA System, Aeverl Medical, Gainesville, Georgia).12,54 This computerized force measurement system is operated by a custom software package (QMA42) run by a Pentium 4 IBM compatible computer. Aluminum uprights and clamps are fixed to an electric hi-lo treatment table to provide points of attachment for an Interface SM250 force gauge (Interface Inc, Scottsdale, Arizona). A signal conditioning unit supplies the force gauge with a 10-V current, amplifies the signal from the strain gauge, converts the analog signal from the strain gauge into a digital value, and processes impulses from the start/stop switch attached to the testing table. The following standard sequence of testing was used to minimize position changes right dorsiflexion, left dorsiflexion, right knee flexion, right knee flexion, right knee extension, left knee extension, right hip extension, left hip extension, left hip flexion, and right hip flexion. Muscle groups were tested in the midrange of the joint with gravity eliminated with the exception of hip flexion and hip extension which were performed in supine with the trunk resting on a 20 degree wedge; thigh supported at 20 degree hip flexion from horizontal by testing strap (hip extension) or towel roll (hip flexion).

Three maximal voluntary isometric efforts were obtained and the maximum value of the 3 valid trials was utilized. Participants held the contractions for 3 to 5 seconds to ensure that maximal effort was reached. A minimum of 5 seconds were allowed to elapse between trials. Participants were encouraged with consistent enthusiasm to “push” or “pull” against the strap with all of their strength. They were not permitted to stabilize themselves by holding onto the table. Standard limb positions and stabilization techniques were utilized.55 Intra and interrater reliability of this approach has been established for multiple populations with neuromuscular disease.56–58

Mobility Assessment

Mobility was assessed using the Timed up and Go (TUG),10-m walk test at both a self-selected (TMWSST) and maximal-pace (TMWMP),60,61 time to ascend (S-A) and descend (S-D)62 one flight (10 steps) of stairs and a 6-Minute Walk Test (6MWT).

For the TUG, participants were instructed to start from a seated position and rise to standing, walk forward 3 m, turn around, and return to sitting as quickly as possible. Time was recorded to the nearest 0.01 second from the time of the word “go” until return contact with the buttocks on the chair. The mean of 3 trials was recorded for analysis. The TUG has been shown to be related to increased risk of falls for older adults requiring greater than 13.5 seconds to complete the test.63 For the 10-m walk test, participants were instructed to start from a stationary standing position. Following a “go” signal the participant walked over a 16-m walkway. Three trials were performed at the self-selected speed, followed by 3 trials at maximal safe speed. Time required to traverse the middle 10 m of the walk was recorded to avoid acceleration and deceleration effects. Time was recorded to the nearest 0.01 second as the center of mass crossed over the initial 10-m mark (start of recording) until the center of mass crossed over the final 10-m mark (end of recording). High test-retest reliability has been reported for this test in individuals with stroke64 and in individuals with neurologic disorders (ICC = 0.87).65

For the S-A and S-D, participants were instructed to ascend and descend one flight of stairs (10 steps) under close supervision as quickly and safely as possible. Participants could use the handrail(s) if they typically would use them. Time was recorded to the nearest 0.01 second from a verbal “go” signal to final foot placement on the top/bottom step. Two trials were performed and the mean was recorded. Validity measures have been reported previously.62

The 6MWT measures the distance a subject can walk in 6 minutes to assess walking ability in activities of daily living.66 Participants were instructed to cover as much distance as possible in 6 minutes utilizing their usual assistive device(s). Distance was recorded to the nearest 0.50 m. This measure has been validated in healthy elderly participants for assessment of physical capacity.67 Intra- and interrater reliability (ICC = 0.95, ICC = 0.91, respectively) has been assessed in individuals with MS.68

Balance Assessment

The Berg Balance Scale (BBS)69 is a measure of static standing balance. It is composed of 14 items that are performed without the use of upper extremity support. Participants were rated from 0 to 4 on ability to perform the task with a maximum numerical score of 56. Intra- and interrater reliability (ICC = 0.99, ICC = 0.94, respectively) has been assessed in individuals with MS.70,71

Fatigue Assessment

The Fatigue Severity Scale (FSS) is a self-report measure designed to assess the impact of fatigue on daily function.72 The scale is composed of 9 items that relate to daily activities. Participants rated how fatigue impacts the 9 activities using a 7-point scale (wherein 1 indicates “strongly disagree” and 7 indicates “strongly agree” with the statement). The FSS has been shown to have a high degree of internal consistency (Cronbach α = 0.81), validity and sensitivity to clinical change in individuals with MS.72

Statistical Analysis

Data analysis was performed with SPSS Version 17.0 (SPSS Inc, Chicago, Illinois) for Windows. The assumptions of parametric statistics were assessed via tests of normality and homogeneity of variance and homogeneity of slopes. In all cases, the assumptions were met; therefore, parametric tests were performed. We examined mean baseline demographic characteristics, including age, Expanded Disability Status Score (EDSS), duration of disease, body mass index, and TUG values utilizing an independent samples t test to determine if there were demographic differences between the groups prior to their participation. A repeated-measure ANOVA (RMANOVA) was conducted. An independent variable of group had 2 levels (STAND...
and RENEW) over 2 time periods (pre- and posttraining). A RMANOVA was performed for the mean of each dependent variable of strength, mobility, balance, and fatigue. The time main effect and the group × time interaction were tested using the multivariate criterion of Wilks’ lambda (Λ). The level of significance was set at $P < 0.05$. No adjustments were made to the $P$ level for these tests because of the exploratory nature of this study. The pre- and postintervention means for each outcome variable of strength, mobility, balance, and fatigue (FSS; tUG, Timed Up and Go; s, seconds; TMWSS, 10-m walk self-selected pace expressed in m/s; TMWMP, 10-m walk maximum pace; 6MWT, 6-Minute Walk Test; BBS, Berg Balance Scale; FSS, Fatigue Severity Scale; kg, kilogram; Ext, extension; L, left; R, right). Strength SUM was analyzed last.

### RESULTS

Twenty individuals completed the initial testing and began training; one individual in the RENEW group did not continue with the training after 6 weeks because of difficulty committing to 3 days per week schedule. On average, individuals in both groups participated in 30 of 36 days of exercise (82% participation). No adverse events occurred in the RENEW group. One individual in the STAND group reported exercise (82% participation). No adverse events occurred in the RENEW group.

Our 2 groups at pretesting for our outcome measures; strength (overall strength; $t_{11} = 0.34, P = 0.74$), mobility (TMWSS; $t_{17} = 0.07, P = 0.94$), balance (BBS; $t_{17} = -1.06, P = 0.31$) and fatigue (FSS; $t_{17} = -0.49, P = 0.63$).

#### Strength Results

A significant time effect was observed for knee flexion left ($\Lambda = 0.78, F_{1,17} = 4.54, P < 0.05$), for knee extension left for the RENEW group ($\Lambda = 0.67, F_{1,17} = 8.44, P = 0.01$) and for STAND group for hip flexion left ($\Lambda = 0.74, F_{1,16} = 5.75, P = 0.03$). No significant interactions were observed for any strength measure in the RMANOVA (Table 1). The mean difference in sum strength in the RENEW group was 38.60 representing a 15% increase with a 95% confidence interval ($-26.55$ to 103.75) compared to the sum strength observed in the STAND group with a mean difference of 5.58 or a 2% increase and a 95% confidence interval ($-22.98$ to 34.15).

#### Mobility Results

No significant time effects or interactions were observed for the following mobility measures; TUG, TMWSS, TMWM, and 6MWT with the RMANOVA (Table 1). No significant time effect was observed for S-A, S-D; but a significant interaction was observed for both stair ascent, $\Lambda = 0.72, F_{1,16} = 6.38, P = 0.02$ and stair descent, $\Lambda = 0.72, F_{1,16} = 6.42, P = 0.02$. The interaction shows the STAND group improved more than RENEW for both stair ascent and descent (Table 1).

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**Table 1. Mean Pre- and Post-Testing Values for RENEW and STAND Groups for Each Dependent Variable, Within Group Mean Difference (MD) with 95% Confidence Interval and $P$-Value for Interaction Effect**

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>Pre</th>
<th>Post</th>
<th>Within-group MD (95% CI)</th>
<th>Interaction ($P$)</th>
<th>Pre</th>
<th>Post</th>
<th>Within-group MD (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mobility measures</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>TUG (s)</td>
<td>15.29</td>
<td>15.49</td>
<td>0.20 (−1.72 to 2.12)</td>
<td>0.81</td>
<td>14.65</td>
<td>15.34</td>
<td>0.69 (−3.44 to 4.83)</td>
</tr>
<tr>
<td>TMWSS (m/s)</td>
<td>0.84</td>
<td>0.87</td>
<td>0.03 (−0.09 to 0.15)</td>
<td>0.96</td>
<td>0.83</td>
<td>0.87</td>
<td>0.04 (−0.06 to 0.13)</td>
</tr>
<tr>
<td>TMWM (m/s)</td>
<td>1.06</td>
<td>1.05</td>
<td>−0.01 (−0.10 to 0.08)</td>
<td>0.15</td>
<td>1.10</td>
<td>1.19</td>
<td>0.09 (−0.03 to 0.22)</td>
</tr>
<tr>
<td>Stair ascent (s)</td>
<td>9.23</td>
<td>9.47</td>
<td>0.24 (−1.32 to 1.81)</td>
<td>0.02</td>
<td>15.94</td>
<td>13.77</td>
<td>−2.17 (−3.69 to −0.65)</td>
</tr>
<tr>
<td>Stair descent (s)</td>
<td>10.23</td>
<td>10.59</td>
<td>0.36 (−1.41 to 2.12)</td>
<td>0.02</td>
<td>13.22</td>
<td>10.48</td>
<td>−2.74 (−4.80 to −0.67)</td>
</tr>
<tr>
<td>6MWT (m)</td>
<td>372</td>
<td>409</td>
<td>37 (1.4 to 72.1)</td>
<td>0.89</td>
<td>248</td>
<td>280</td>
<td>32 (−40 to 103)</td>
</tr>
<tr>
<td>Balance measure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BBS (/56 max)</td>
<td>46</td>
<td>47</td>
<td>1.3 (−1.6 to 4.3)</td>
<td>0.049</td>
<td>41</td>
<td>47</td>
<td>6.0 (2.1 to 10)</td>
</tr>
<tr>
<td>Fatigue measure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FSS (/10 max)</td>
<td>6.1</td>
<td>5.1</td>
<td>−0.94 (−1.64 to −0.24)</td>
<td>0.30</td>
<td>5.8</td>
<td>4.5</td>
<td>−1.38 (−2.00 to −0.75)</td>
</tr>
<tr>
<td>Knee flexion L</td>
<td>13.49</td>
<td>16.49</td>
<td>3.00 (−1.85 to 7.85)</td>
<td>0.65</td>
<td>13.00</td>
<td>14.93</td>
<td>1.93 (−0.61 to 4.47)</td>
</tr>
<tr>
<td>Knee flexion R</td>
<td>14.93</td>
<td>16.15</td>
<td>1.21 (−4.73 to 7.16)</td>
<td>0.80</td>
<td>12.18</td>
<td>14.08</td>
<td>1.91 (−0.75 to 4.57)</td>
</tr>
<tr>
<td>Knee Ext. L</td>
<td>27.92</td>
<td>33.51</td>
<td>5.59 (0.40 to 10.78)</td>
<td>0.50</td>
<td>25.27</td>
<td>28.73</td>
<td>3.46 (−1.41 to 8.35)</td>
</tr>
<tr>
<td>Knee Ext. R</td>
<td>30.04</td>
<td>30.95</td>
<td>0.91 (−6.73 to 8.54)</td>
<td>0.88</td>
<td>25.24</td>
<td>26.77</td>
<td>1.53 (−3.59 to 6.65)</td>
</tr>
<tr>
<td>Hip flexion L</td>
<td>30.94</td>
<td>35.79</td>
<td>4.85 (−1.83 to 11.52)</td>
<td>0.47</td>
<td>31.71</td>
<td>34.28</td>
<td>2.57 (0.05 to 5.09)</td>
</tr>
<tr>
<td>Hip flexion R</td>
<td>32.53</td>
<td>36.28</td>
<td>3.76 (−3.87 to 11.39)</td>
<td>0.28</td>
<td>30.72</td>
<td>30.16</td>
<td>−0.56 (−5.13 to 4.01)</td>
</tr>
<tr>
<td>Hip Ext. L</td>
<td>38.07</td>
<td>42.48</td>
<td>4.41 (−3.91 to 12.73)</td>
<td>0.52</td>
<td>38.72</td>
<td>40.34</td>
<td>1.62 (−3.60 to 6.83)</td>
</tr>
<tr>
<td>Hip Ext. R</td>
<td>36.08</td>
<td>42.12</td>
<td>6.04 (−2.94 to 15.03)</td>
<td>0.23</td>
<td>40.21</td>
<td>40.65</td>
<td>0.44 (−4.73 to 5.60)</td>
</tr>
<tr>
<td>Dorsi flexion L</td>
<td>12.32</td>
<td>14.30</td>
<td>1.98 (−3.79 to 7.75)</td>
<td>0.44</td>
<td>16.86</td>
<td>16.98</td>
<td>0.12 (−1.54 to 1.79)</td>
</tr>
<tr>
<td>Dorsi flexion R</td>
<td>15.24</td>
<td>16.69</td>
<td>1.45 (−3.12 to 6.03)</td>
<td>0.95</td>
<td>14.48</td>
<td>15.75</td>
<td>1.27 (−3.26 to 5.81)</td>
</tr>
<tr>
<td>Strength SUM</td>
<td>254.95</td>
<td>293.55</td>
<td>38.60 (−26.55 to 103.75)</td>
<td>0.31</td>
<td>273.39</td>
<td>278.97</td>
<td>5.58 (−22.98 to 34.15)</td>
</tr>
</tbody>
</table>

*TUG, Timed Up and Go; s, seconds; TMWSS, 10-m walk self-selected pace expressed in m/s (m/s); TMWMP, 10-m walk maximum pace; 6MWT, 6-Minute Walk Test; BBS, Berg Balance Scale; FSS, Fatigue Severity Scale; kg, kilogram; Ext, extension; L, left; R, right. Strength SUM was analyzed last.*
A significant interaction (\( \Lambda = 0.79, F_{1,17} = 4.50, P < 0.05 \)) and a significant time effect (\( \Lambda = 0.61, F_{1,17} = 11.10, P < 0.01 \)) was observed for the Berg Balance Scale. The STAND group made greater improvements than the RENEW group accounting for the interaction (Table 1).

### Balance Results

A significant interaction (\( \Lambda = 0.79, F_{1,17} = 4.50, P < 0.05 \)) and a significant time effect (\( \Lambda = 0.61, F_{1,17} = 11.10, P < 0.01 \)) was observed for the Berg Balance Scale. The STAND group made greater improvements than the RENEW group accounting for the interaction (Table 1).

### Fatigue Results

No significant interaction was observed for Fatigue Severity Scale (Table 1); however, a significant time effect was observed, \( \Lambda = 0.35, F_{1,17} = 31.79, P < 0.001 \).

### DISCUSSION

We hypothesized that the use of a high-intensity RENEW exercise program would be associated with increases in muscle strength, which in turn would provide the stimulus for improvements in functional mobility. For this reason, the results observed in this study for strength, mobility, and balance were not as anticipated. Although we observed a 15% increase in overall strength in the RENEW group compared to only a 2% increase in the STAND group; this interaction was not significant (\( P = 0.31 \)) which may be partly because of the large variability observed in the RENEW group as evidenced by the large span in the confidence interval. Furthermore, it appears the strength changes observed in the RENEW group were not beneficial to function as the interactions observed for stair ascent, stair descent, and balance found that the STAND group performed better than the RENEW group. The results of this study differ from our findings from several prior RENEW intervention studies involving populations with various other diagnoses. The same RENEW protocol resulted in greater strength gains and improved mobility as compared to traditional strength training paradigms in these clinical populations. One reason for the different results observed in this study as compared with previous RENEW studies may relate to the amount of variability observed in our participants with MS for all outcome measures.

The RENEW protocol used in this study has previously been shown to be safe and effective for individuals with Parkinson disease.\(^{38}\) Individuals with Parkinson disease participating in the RENEW protocol demonstrated a 29% improvement in muscle strength in the more impaired limb and 19% improvement in the less impaired limb compared to a control group participating in a standard exercise program.\(^{43}\) Furthermore, in the individuals with Parkinson disease, significant improvements in mobility were reported for distance on the 6-Minute Walk Test (21%) as well as decreased time required for stair ascent (18%).\(^{43}\)

The RENEW protocol utilized in this study has also previously been shown to result in greater improvements in strength and function in populations with sarcopenia of various etiologies, such as orthopedic impairments, metabolic conditions, and aging compared to traditional rehabilitation protocols. Individuals 1 to 4 years after total knee arthroplasty (TKA) demonstrated a 15% improvement in knee extensor muscle strength after participating in the RENEW protocol compared to a group of individuals participating in a traditional post-TKA protocol, who showed no increase in knee extensor muscle strength.\(^{47}\) Furthermore, the RENEW group experienced significant (20%) improvements in the mobility tasks, including TUG, 6-minute walk, stair ascent, and stair descent compared to a significant (16%) improvement only in the TUG and stair descent for individuals in the traditional rehabilitation program. Similar results of improvement in strength and mobility have been reported in individuals who have undergone anterior cruciate ligament (ACL) reconstruction after using the RENEW protocol compared to a traditional ACL protocol. Improvements in knee extensor muscles strength were significantly greater in the RENEW compared to the traditional ACL protocol at the end of 12 weeks of training.\(^{73}\) These strength changes persisted at 1 year after surgery with a 33% improvement observed in the RENEW group compared to a 9% improvement observed in the group that received the traditional ACL protocol. Improvements in strength and function have been observed in individuals with sarcopenia as a result of type II diabetes with participation in the RENEW protocol and an aerobic training program compared to an aerobic training program alone.\(^{43}\) Furthermore, significant improvements in knee extensor muscle strength and function (6-minute walk distance and steps taken per day) have been observed in postmenopausal women with impaired glucose tolerance who have participated in the RENEW protocol compared to a group of nonexercise controls.\(^{75}\) A population of frail elders with a history of falls participating in the RENEW protocol demonstrated a significant (60%) increase in isometric knee extension strength compared to a nonsignificant (15%) increase for individuals participating in a traditional exercise program.\(^{38}\) Overall prior studies on other populations using the same RENEW protocol as described in this study have

### Table 2. Participant Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>All (N = 19) Mean (SD)</th>
<th>Median</th>
<th>Range</th>
<th>Stand (N = 10) Mean (SD)</th>
<th>Renew (N = 9) Mean (SD)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>48.9 (11.14)</td>
<td>50</td>
<td>23-66</td>
<td>49.7 (10.98)</td>
<td>48.0 (11.19)</td>
<td>0.75</td>
</tr>
<tr>
<td>Sex</td>
<td>8 men 11 women</td>
<td></td>
<td></td>
<td>4 men 6 women</td>
<td>4 men 5 women</td>
<td></td>
</tr>
<tr>
<td>EDSS pre</td>
<td>5.24 (0.96)</td>
<td>6.0</td>
<td>3.5-6.5</td>
<td>5.15 (0.97)</td>
<td>5.33 (1.00)</td>
<td>0.69</td>
</tr>
<tr>
<td>Duration of disease, months</td>
<td>145.8 (97.5)</td>
<td>144</td>
<td>5-360</td>
<td>142.2 (87.6)</td>
<td>149.9 (113.8)</td>
<td>0.88</td>
</tr>
<tr>
<td>BMI pre, kg/m²</td>
<td>29.9 (6.5)</td>
<td>30.2</td>
<td>19.7-44.1</td>
<td>31.9 (7.9)</td>
<td>28.1 (4.5)</td>
<td>0.22</td>
</tr>
<tr>
<td>6MWT pre, seconds</td>
<td>14.95 (10.42)</td>
<td>9.73</td>
<td>7.25-46.41</td>
<td>14.65 (12.02)</td>
<td>15.29 (9.03)</td>
<td>0.90</td>
</tr>
</tbody>
</table>

\(^{a}\)Values are expressed as mean (SD) except when noted. Significance was set at \( P = 0.05 \). EDSS, Expanded Disability Status Score; TUG, Timed Up and Go; 6MWT, 6-Minute Walk Test.
consistently demonstrated an improvement in strength with the use of this high-intensity training. The same RENEW protocol was not associated with a significant change in strength nor function in this study of individuals with MS.

Interestingly, strength gains have been more consistently reported in low-intensity resistance training studies in individuals with MS whereas the functional gains have not been as consistent. An aerobic and circuit training program increased isometric knee flexion and extension strength compared to an inactive control group; however, functional changes were variable. No changes were observed in balance whereas improvements in walking speed and endurance were observed for the exercise group. A study utilizing a progressive resistance exercise-training program ranging from 60% to 80% of 1-RM reported increases in strength with varying functional improvements. Changes were reported on the 10-m fast walk test, but not on the 10-m self-selected walk test or a 2-minute walk test or a timed stairs walk. Another study utilizing progressive resistance exercise training ranging from 40% to 70% of 1-RM reported increases in strength and functional improvements in mobility, and walking endurance.

One outcome measure that appears to demonstrate consistent improvement in individuals with MS after an exercise program is a decrease in perception of fatigue. A decrease in fatigue has been reported in aerobic training studies, and this complex interaction of central and peripheral fatigue and muscle capacity observed in individuals with MS and this complex interaction may complicate the relationship of improved strength and concomitant functional improvements.

Limitations

Limitations to this study include variability in the level of disability of individuals with MS from mild to moderate severity. A more homogenous subset of individuals based on severity of disability may have produced different results. It is possible that individuals with mild disease impairment may benefit from a high-intensity ergometric resistance training program and individuals with more moderately to severe disease may not.

Another limitation of this study relates to the great variability of the clinical presentation of our study participants. This variability potentially limited our ability to detect changes in strength and function within each group. The power calculations of this study were based on prior RENEW studies, which demonstrated large effect sizes between groups for both strength and functional changes. The MS patient population typically shows great heterogeneity in clinical presentation and this variability should be accounted for in future research involving persons with MS. Therefore, if we were to repeat this study anticipating the same variability, we would need 43 participants per group to potentially detect a significant interaction between groups. This calculation was determined by using the sum strength mean differences and SDs reported in this current study based on the observed effect size in this study of 0.65 and power of 0.80 and a .05. Another limitation was not assessing the individuals during the 12-week training program to determine the strength and functional changes across time. It could be that the training was too long or not long enough to appreciate the benefits. A 14- to 30-day follow-up may also have provided insight into the long-term effects of this training, specifically recovery related to function.

Future research is warranted to elucidate the impact of resistance training for individuals with MS of varying levels of disability across the time course of the disease. Further studies are needed to increase our understanding of optimal exercise dosing to improve strength and function in muscles with varying levels of neurogenic weakness in individuals with MS.

CONCLUSIONS

Individuals with multiple sclerosis were able to tolerate a RENEW training program; however, the results observed were different than anticipated. Although prior research has supported the benefit of RENEW in multiple populations with sarcopenia, the same high-intensity resistance training program did not result in significant improvements in strength, and was not as effective as standard exercise alone for improving stair ascent/descent ability or balance in this group of individuals with MS. Limitations in strength gains may have been
because of neurogenic weakness, possibly limiting the value of RENEW. Determining the most effective training program to create positive changes in individuals with MS throughout the various stages of the disease warrants further exploration.

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