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*Original Research*

# Effects of Creatine Supplementation and Progressive Resistance Training in Stroke Survivors

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ABSTRACT

***International Journal of Exercise Science 15(2): 1117-1132, 2022.*** The purpose was to investigate the effects of progressive resistance training (PRT) and creatine supplementation in stroke survivors. Participants were randomized to one of two groups: creatine ($n$ = 5; 51 ± 16y) or placebo ($n$ = 3; 73 ± 8y) during 10 weeks of supervised PRT. Prior to and following PRT and supplementation, assessments were made for body composition (lean tissue and fat mass), muscle thickness, muscle strength (1-repetition maximum), functional exercise capacity (6-minute walk test, Berg Balance Scale; BBS), cognition (Montreal Cognitive Assessment; MoCA), and symptoms of anxiety (Generalized Anxiety Disorder Assessment-7; GAD-7) and depression (Center for Epidemiological Studies Depression Scale; CES-D). There were time main effects for leg press strength (increased; $p$ = 0.001), chest press strength (increased; $p$ = 0.003), elbow flexor muscle thickness (increased; $p$ = 0.007), BBS (increased; $p$ = 0.002), MoCA (increased; $p$ = 0.031) and CES-D (decreased; $p$ = 0.045). There was a group x time interaction for the 6 minute walk test ($p$ = 0.039). The creatine group significantly increased walking distance over time ($p$ = 0.002) with no change in the placebo group ($p$ = 0.120). Ten weeks of PRT had some positive effects on measures of muscle strength and size, balance, cognition and depression. The addition of creatine to PRT significantly improved walking performance in stroke survivors.

KEY WORDS: Medical, strength, functional exercise capacity, muscle mass

## INTRODUCTION

Approximately 25% of individuals will suffer a stroke in their lifetime (36). The annual medical costs associated with stroke are estimated to be $184 billion by 2030, inevitably placing substantial burden on the healthcare system (31). Stroke survivors experience reductions in muscle mass, strength and functional exercise capacity (7, 14) and increased symptoms of

anxiety and depression (38), resulting in long-term disability and reduced quality of life (46). Stroke adversely affects muscle structure by increasing the loss of muscle fibers (as a result of loss of motor units), increasing inflammation and activation of catabolic pathways, and shifting muscle fiber-types from slow to fast, resulting in greater muscle fatigue and reduced gait performance (50). As a possible countermeasure, the combination of progressive resistance training (PRT) and creatine supplementation may serve as an effective rehabilitation intervention for stroke survivors.

PRT has been shown to be a safe and effective intervention for improving measures of muscle mass and strength (4, 14, 43, 49), functional exercise capacity (35) and decreasing symptoms of anxiety and depression in stroke survivors (1, 20, 40). Supplementing with creatine monohydrate may augment these benefits, possibly by creatine influencing processed involved in anaerobic energy metabolism, muscle protein kinetics and inflammation (18, 22, 39). Two meta-analyses have been performed showing that creatine supplementation in conjunction with PRT increased muscle mass and strength and a measure of functional exercise capacity (sit-to-stand performance) more than placebo and PRT in older adults (18, 22). Emerging evidence suggests that creatine supplementation may reduce symptoms of anxiety and depression, possibly by influencing brain energy production, storage, and utilization therefore acting as a spatial energy buffer (37). However, the effects of PRT and creatine supplementation in stroke survivors are unknown. Therefore, the primary purpose of this study was to examine the effects of PRT and creatine supplementation on body composition, limb muscle thickness, strength, tasks of functional exercise capacity, cognition and symptoms of anxiety and depression in stroke survivors. A secondary purpose was to monitor any adverse events from PRT and/or creatine supplementation to determine the feasibility and safety of this intervention. It was hypothesized that the combination of PRT and creatine supplementation would lead to greater benefits compared to placebo and PRT.

## METHODS

*Participants*

Individuals (≥ 30 years of age) who were medically diagnosed with having a first-time stroke and able to walk without an assistive device were eligible to participate. Eligible participants were then excluded if they were taking dietary supplements that contained creatine monohydrate ≤ 12 weeks prior to the start of the study; if they had a diagnosed neurological disorder (i.e. Dementia, Parkinson's Disease), or if they had pre-existing kidney or liver abnormalities. Before the start of the study, participants were required to obtain medical clearance, disclose all current medications and past medical history and complete a Physical Activity Scale for Individuals with Physical Disabilities (PASIPD) questionnaire which assessed leisure, household, and work-related physical activity over 7 days, including frequency and duration. The average number of hours that a specific task was completed was multiplied by a metabolic equivalent (MET) value associated with the intensity of the activity. Scores ranged from 0 (no activity) to > 100 METS · hours/day (54). Participants also completed the Stroke Impact Scale (SIS), a stroke-specific, self-report, health status measurement, which was designed

to assess multidimensional stroke outcomes (34). Participants were instructed not to alter their diet or engage in additional physical activity or PRT that was not part of the study design. The multi-site randomized, double-blind, placebo-controlled trial (ClinicalTrials.gov Identifier: *NCT03941678)* was approved by the ethics review boards at the Universities of Regina and Saskatchewan. All participants were informed of the potential risks and the purpose of the study before their written consent was obtained. Furthermore, this manuscript strictly adheres to the ethical policies established by the International Journal of Exercise Science editorial board (45).

*Protocol*

Participants were matched according to age, sex, ischemic (defined as an interruption of blood supply to any part of the brain resulting in loss of function) or hemorrhagic stroke (defined as a rupture of a blood vessel or an abnormal vascular structure) (5) and body mass. After exclusion criteria was applied, participants were randomized on a 1:1 basis to one of two groups: creatine (CR) or placebo (PLA; corn-starch maltodextrin). The primary dependent variables measured at baseline and after 10 weeks of PRT and supplementation were: 1) body composition (whole-body lean tissue and fat mass), 2) elbow and knee flexor and extensor muscle thickness, 3) upper- and lower-body muscle strength, 4) measures of functional exercise capacity, 5) test of cognition, and 6) symptoms of anxiety and depression. In addition, participants were asked to complete a 3-day food record during the first and final week of the study to determine whether total energy and macronutrient composition changed over the duration of the study.

Creatine monohydrate (Creapure® AlzChem Trostberg GmbH, Germany) and placebo (Globe Plus 10 DE Maltodextrin, Univar Canada) were administered in study kits. Each kit contained the participant's supplement for the duration of the study, measuring spoons (ranging from 1/8 teaspoon to 1 tablespoon) and detailed instructions on which and how many spoons to consume per day. Contents of the Creapure® were verified by an independent laboratory (The Cary Company, Addison, Ill., USA) with purity being > 99.9%. For days 1-7, participants ingested 0.3 $g \cdot kg^{-1} \cdot d^{-1}$ of creatine (0.075 $g \cdot kg^{-1} \cdot d^{-1}$ x 4 times daily) as this loading strategy is effective for increasing intramuscular creatine stores (33). Thereafter, participants consumed 0.1 $g \cdot kg^{-1} \cdot d^{-1}$ as this maintenance dosage has been shown to have favorable effects on muscle mass and strength in older adults (19, 23). On training days, participants consumed their supplement (mixed in water) immediately after each training session, as post-exercise creatine supplementation may lead to slightly greater gains in muscle accretion compared to pre-exercise creatine supplementation (27). On non-training days, the supplement was consumed with food. Adherence with the supplementation protocol was assessed by compliance logs. Upon completion of the study, participants were asked whether they believed they were consuming creatine or placebo.

Before the start of supplementation, participants performed three supervised familiarization sessions, on non-consecutive days, with the resistance training equipment in private training facilities at the Universities of Regina and Saskatchewan. Three familiarization training sessions, with repeated testing trials, produce reliable strength measurements (48). All exercises were performed bilaterally as this is a safe and effective rehabilitation strategy for stroke patients (53).

During these familiarization sessions, participants were shown how to properly use the machine-based resistance training equipment and perform 3 sets of 10 repetitions per exercise (Pulse Exercise Systems Inc., Winnipeg, Canada; Life Fitness; Franklin Park, IL).

Supplementation commenced following the first progressive resistance training (PRT) session. Each PRT was supervised, and participants initially completed a 5-10 minute warm up on a cycle ergometer, followed by light static stretching. Participants then performed 3 sets of ~10 repetitions at 70% baseline 1-RM for each exercise, 2 times per week, on non-consecutive days, for 10 weeks. Ten weeks of supervised PRT was chosen because this length of training has favorable effects on measures of muscle mass and strength in older adults (19). To ensure progression, once 3 sets of 10 repetitions could be completed for an exercise using a constant training load, the weight was increased (by 2-5 kg) and held constant until a subsequent 3 sets of 10 repetitions could be completed. This progressive strategy (per exercise) was used for the duration of the study. During each training session, participants filled out training logs where they recorded the load used and number of sets and repetitions performed for each exercise. These logs were subsequently used to determine total training volume load (weight x sets x repetitions) performed over time.

Lean tissue and fat mass were assessed by dual-energy X-ray absorptiometry in array mode (DXA; QDR Discovery Wi, Hologic, Inc., Bedford, MD) using procedures previously described [26]. Both universities have the same Hologic Discovery system and the same nuclear medicine technologist at each institution performed the pre- and post-testing scans. The coefficients of variation from previous research in older adults were 1.0% for lean tissue mass and 2.9% for fat mass (24).

Muscle thickness (right side and left side) of the elbow and knee flexor and extensor muscle groups was measured using B-Mode ultrasound (LOGIQe, GE Medical Systems Co., Wuxi, China) as previously described (15). Both universities have the same LOGIQe, GE Medical System ultrasound and the same researcher at each institution performed both pre- and post-testing measurements. The coefficients of variation from previous research in older adults were 2.6% for elbow flexors, 2.1% for elbow extensors, 2.3% for knee flexors and 2.1% for knee extensors (16).

Bilateral leg press and chest press strength (Pulse Exercise Systems Inc., Winnipeg, Canada; Life Fitness; Franklin Park, IL) was assessed using a 1-repetition maximum (1-RM) standard testing procedure as previously described (24). The coefficients of variation from previous research in older adults were 3.0% for leg press and 3.6% for chest press (24).

The 6-minute walk test and the Berg Balance Scale (BBS) test were used to assess functional exercise capacity. The 6-minute walk test measured the distance participants could walk in 6 minutes on a 30 meter course. Prior to the start of the test, participants sat on a chair for 10 minutes. Participants then stood and walked as fast as they could (without running) along the

30 meter course. Once the 6 minutes was complete, the number of meters the participant walked was recorded.

The BBS test was used to objectively determine the participant's ability to maintain balance (8). The BBS contained 14 tasks involving mobility and balance which were scored using a 5-point ordinal scale ranging from 0-4, with 0 indicating the lowest level of function and 4 indicating the highest level of function. The BBS shows high reliability (interclass correlation coefficient; 0.92-0.98) in stroke patients (11).

The Montreal Cognitive Assessment (MoCA) was used to assess cognition. The MoCA assessed short term memory, executive function, language, visuospatial abilities, attention and concentration and orientation to time and place (44). The Generalized Anxiety Disorder Assessment (GAD-7) questionnaire was used to assess symptoms of anxiety. This self-report questionnaire asked participants to rate their symptoms over the past two weeks (52). The Center for Epidemiological Studies Depression Scale (CES-D) was used to assess symptoms of depression. The CES-D asked participants to rate how often over the past week they experienced symptoms of depression (6). Dietary intake was recorded during the first and final week of PRT and supplementation to assess differences in total energy (kcal) and macronutrient composition between groups over time. MyFitnessPal (http://www.myfitnesspal.com) was used to analyze average kcal, carbohydrate, fat, and protein consumption (42).

*Statistical Analysis*

A 2 groups (creatine vs. placebo) x 2 time (baseline vs. 10 weeks) repeated measures ANOVA was used to determine differences between groups over time for the primary dependent variables. After finding a significant difference over time between groups for the 6-minute walking test, we also conducted an ANCOVA with baseline scores as a co-variate for this outcome to ensure differences over time between groups were not affected by baseline differences. A paired sample *t*-test was used to determine differences in dietary intake in the creatine group over time. An independent sample *t*-test was used to compare the volume of resistance training performed between groups. Significance was set *a priori* at an alpha level of $p < 0.05$. Results are expressed as means (standard deviation) or means [95% confidence intervals]. The magnitude of the difference between significant means was determined by eta squared ($\eta^2$). This is a measure of the effect size and therefore of the proportion of the total variance that can be explained by the effects of the treatment. A $\eta^2$ value of 0.15 represents large differences, 0.06 represents medium differences, and 0.01 represents small differences. Statistical analyses were performed using IBM® SPSS® Statistics, v. 26 (Chicago, IL).

## RESULTS

Nine participants were randomized into the study (see Figure 1 for a summary of recruitment, allocation and analysis and Table 1 for descriptive measures). Prior to the start of PRT and supplementation, one participant withdrew due to time constraints unrelated to the study. Therefore, eight participants (CR = 5, PLA = 3) completed the study. Two participants were in

the acute stage (CR = 2; ≤ 6 months since stroke) and six participants were in the chronic stage of stroke recovery (CR = 3, PLA = 3; > 6 months since stroke). Stroke affected the left side in five participants (CR = 4, PLA = 1) and the right side in 3 participants (CR = 1; PLA = 2). Six participants (CR = 5, PLA = 1) were able to provide 3-day food records during the first and final week of PRT and supplementation.

Following the intervention, participants were asked whether they believed they were randomized into the creatine or placebo group. Three of the five participants in the CR group correctly guessed they were receiving creatine and two participants incorrectly guessed. In the PLA group, two participants correctly guessed they were receiving placebo while one participant incorrectly guessed. Training compliance was similar between groups over time (CR: 19/20 sessions completed or 95%; PLA: 19/20 or 95%). Supplementation compliance, based on participant's entries in their logs, was similar between groups over time (CR: 69/70 days or 99%; PLA: 68/70 days or 98%). There were no adverse events reported during the study.

There was no change over time in the CR group for total energy (mean [95% confidence interval]: pre: 1911 kcal [1400, 2422], post: 1896 kcal [1313, 2480], $p$ = 0.904, $\eta^2$ = 0.004, observed power = 0.051), carbohydrate (pre: 226 g [151, 300], post: 222 g [143, 301], $p$ = 0.844, $\eta^2$ = 0.011, observed power = 0.053), fat (pre: 73 g [44, 102], post: 64 g [51, 78], $p$ = 0.482, $\eta^2$ = 0.131, observed power = 0.093) or protein (pre: 86 g [66, 106], post: 89 g [62, 117], $p$ = 0.48, $\eta^2$ = 0.131, observed power = 0.093). Changes for the participant in the PLA group were: total energy (pre: 2074 kcal, post: 2021 kcal), carbohydrate (pre: 148 g, post: 147 g), fat (pre: 86 g, post: 77 g) and protein (pre: 177 g, post: 185). There were no significant differences between groups for the total volume of resistance training performed over the 10 weeks of training (CR: 202680 kg [152458, 252901]; PLA: 152677 kg [32532, 272821]; $p$ = 0.164, $\eta^2$ = 0.295, observed power = 0.267).

There were time main effects for leg press strength (increased; $p$ = 0. 001, $\eta^2$ = 0.836, observed power = 0.995; Figure 2), chest press strength (increased; $p$ = 0.003, $\eta^2$ = 0.785, observed power = 0.971; Figure 3), elbow flexor muscle thickness (increased; left side: $p$ = 0.007, $\eta^2$ = 0.732, observed power = 0.918; right side: $p$ = 0.007, $\eta^2$ = 0.731, observed power = 0.916; Table 2), right side muscle thickness (increased; elbow and knee flexor and extensor muscle groups combined; $p$ = 0.025, $\eta^2$ = 0.668, observed power = 0.719), BBS (increased; $p$ = 0.002, $\eta^2$ = 0.830, observed power = 0.993), MoCA (increased; $p$ = 0.031, $\eta^2$ = 0.568, observed power = 0.651) and CES-D (decreased; $p$ = 0.045, $\eta^2$ = 0.515, observed power = 0.561) (Table 3).

There was a group x time interaction for the 6-minute walk test ($p$ = 0.039, $\eta^2$ = 0.536, observed power = 0.596). The creatine group significantly increased walking distance over time ($p$ = 0.002; [95%CI: -55.0, -23.4]) with no change in the placebo group ($p$ = 0.120; [95%CI: -42.3, 10.3]) (Figure 4). To ensure differences over time between groups for walking distance were not affected by baseline scores, we also conducted an ANCOVA with baseline scores as the co-variate. Using baseline scores as a co-variate, the adjusted post-intervention scores were different between groups (CR: 557 ± 12 m; PLA: 524 ± 11 m).

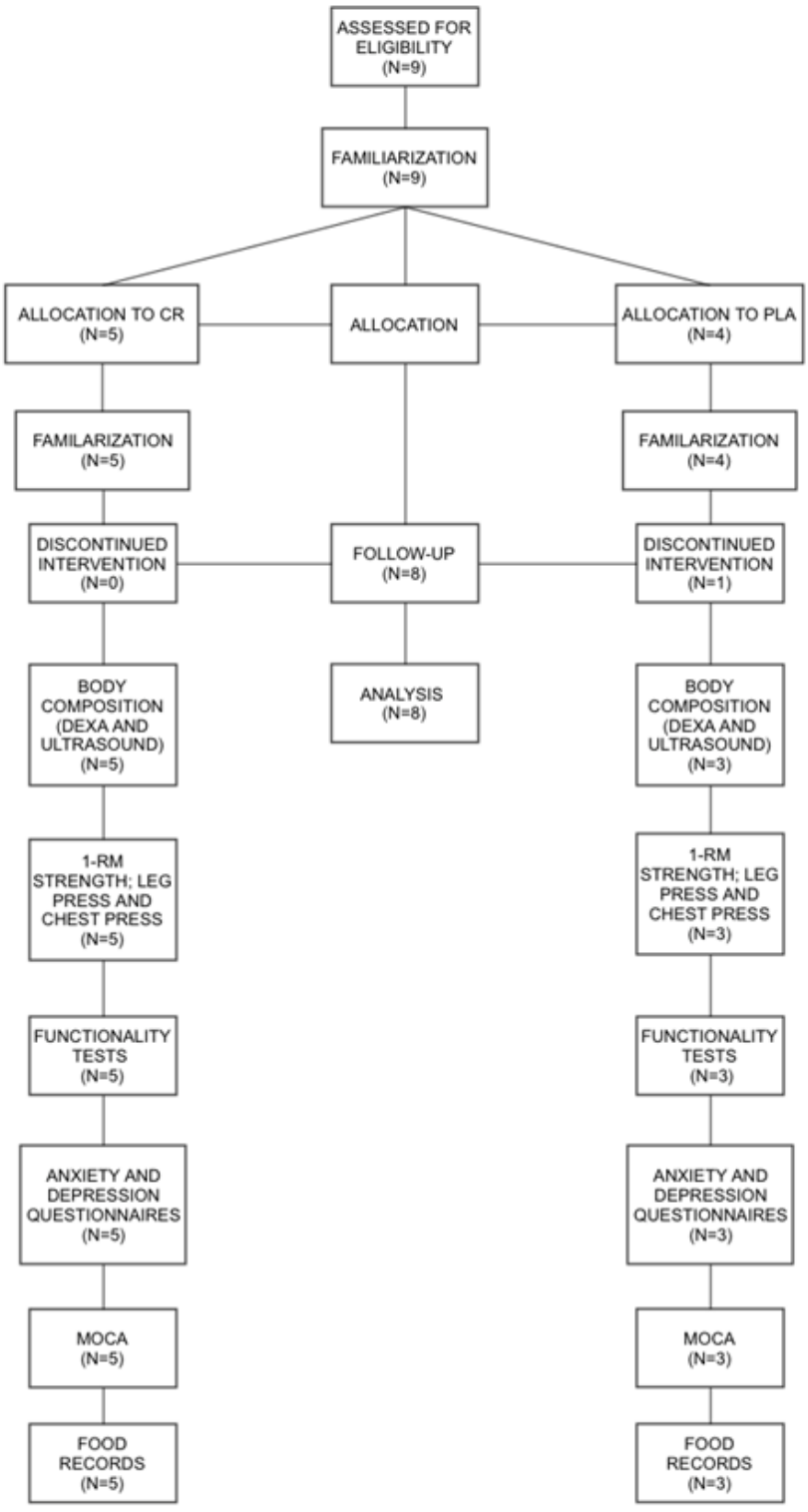


**Figure 1.** Participant flow through RCT.

**Table 1**. Baseline data

| Variable | Creatine | Placebo | *p*-value |
|---|---|---|---|
| Age (yrs) | 51 (16) | 69 (12) | 0.108 |
| Height (cm) | 173 (11) | 172 (5) | 0.847 |
| Body mass (kg) | 84.7 (19.2) | 79.6 (13.4) | 0.666 |
| Physical activity scale | 19.48 (9.52) | 18.06 (6.43) | 0.806 |
| *Stroke impact scale* | | | |
| Strength | 59 (19) | 56 (18) | 0.789 |
| Hand function | 50 (16) | 55 (20) | 0.746 |
| Mobility | 49 (11) | 48 (10) | 0.962 |
| ADL | 57 (23) | 69 (10) | 0.361 |
| Emotion | 72 (8) | 71 (9) | 0.750 |
| Memory | 76 (5) | 68 (14) | 0.256 |
| Communication | 65 (15) | 77 (9) | 0.200 |
| Social Participation | 65 (13) | 73 (6) | 0.296 |
| Global Assessment of Recovery | 75 (19) | 70 (9) | 0.652 |
| Fat mass (kg) | 25.99 (7.56) | 23.04 (11.67) | 0.659 |
| *Lean tissue mass (kg)* | 49.77 (14.19) | 48.78 (8.35) | 0.906 |
| *Muscle thickness(cm)* | | | |
| Left elbow flexor | 3.31 (0.68) | 3.85 (1.21) | 0.423 |
| Right elbow flexor | 3.09 (0.52) | 3.28 (0.68) | 0.642 |
| Left elbow extensor | 3.07 (0.82) | 3.69 (1.24) | 0.400 |
| Right elbow extensor | 3.49 (0.64) | 3.57 (1.07) | 0.895 |
| Left knee flexor | 3.87 (0.31) | 3.98 (1.18) | 0.860 |
| Right knee flexor | 3.72 (0.58) | 4.28 (1.05) | 0.388 |
| Left knee extensor | 3.68 (0.64) | 3.93 (0.97) | 0.652 |
| Right knee extensor | 3.59 (0.56) | 3.71 (0.91) | 0.817 |
| Left Side | 14.53 (1.37) | 14.96 (4.69) | 0.676 |
| Right Side | 13.83 (1.96) | 14.02 (2.86) | 0.582 |
| Appendicular | 24.93 (8.09) | 28.98 (7.53) | 0.324 |
| *Muscle Strength (kg)* | | | |
| Leg press | 170 (63) | 125 (39) | 0.252 |
| Chest press | 51 (34) | 40 (17) | 0.588 |
| *Functional Exercise Capacity* | | | |
| 6-Minute walk (m) | 598.80 (168.93) | 400.25 (53.85) | 0.061 |
| BBS | 53.60 (1.52) | 51.25 (2.99) | 0.166 |
| *Cognition* | | | |
| MoCA | 24.20 (2.59) | 24.00 (3.56) | 0.925 |
| *Anxiety and Depression* | | | |
| GAD-7 | 4.80 (3.83) | 3.00 (2.58) | 0.450 |
| CES-D | 18.80 (6.76) | 17.50 (3.11) | 0.735 |

Values are means (standard deviation). ADL: Activities of daily living; BBS: Berg Balance scale; MoCA: Montreal Cognitive Assessment; GAD-7: Generalized Anxiety Disorder Assessment; CES-D: Center for Epidemiological Studies Depression Scale

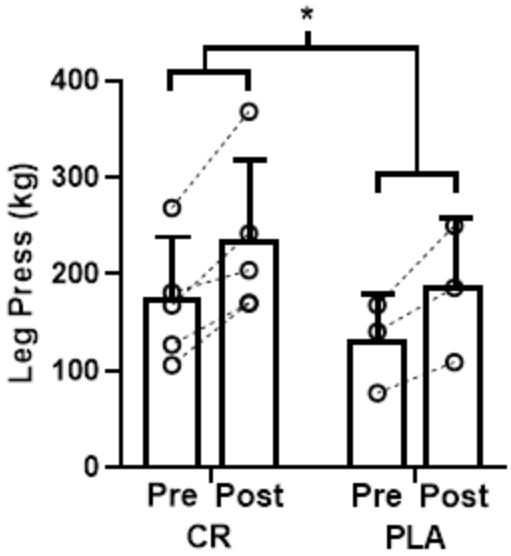


**Figure 2.** Means at baseline (pre) and 10 weeks (post) for leg press strength (kg). Vertical lines represent standard deviation. *Time main effect ($p$ = 0.001).

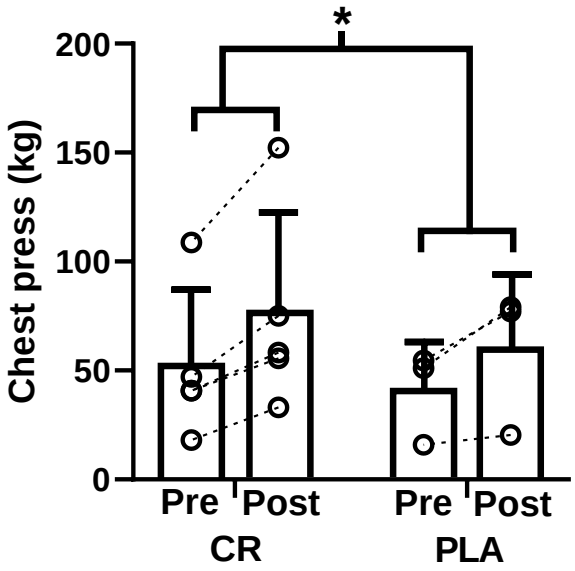


**Figure 3.** Means at baseline (pre) and 10 weeks (post) for chest press strength (kg). Vertical lines represent standard deviation. *Time main effect ($p$ = 0.003).

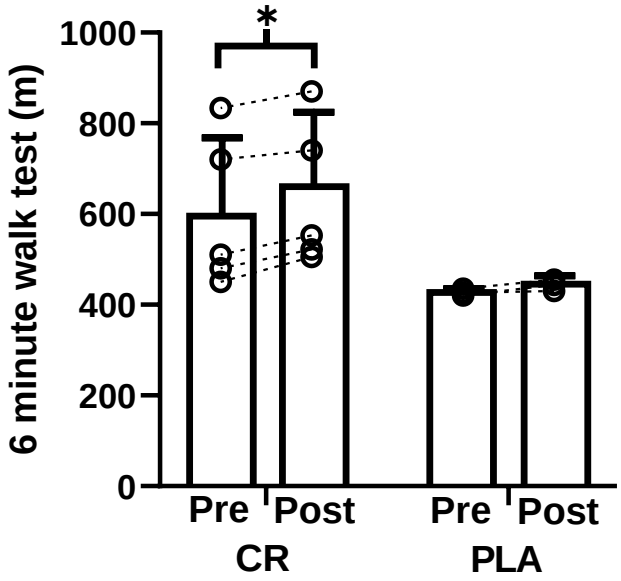


**Figure 4.** Means at baseline (pre) and 10 weeks (post) for the 6-minute walk test (m). Vertical lines represent standard deviation. *Creatine group experienced a significant increase over time ($p$ = 0.039), with no change for the placebo group ($p$ = 0.120).

**Table 2.** Means (95% confidence intervals) at baseline and 10 weeks for measures of body composition.

| | Creatine ($n$ = 5) | | Placebo ($n$ = 3) | |
|---|---|---|---|---|
| | Baseline | 10 weeks | Baseline | 10 weeks |
| Body mass (kg) | 84.7 (67.1, 102.3) | 84.8 (69.1, 100.5) | 73.3 (50.6, 96.0) | 73.4 (53.1, 93.6) |
| Fat mass (kg) | 25.9 (18.9, 33.0) | 25.7 (17.8, 33.6) | 17.3 (8.2, 26.3) | 16.6 (6.4, 26.8) |
| Lean tissue mass (kg) | 49.7 (35.5, 63.9) | 50.9 (36.8, 65.0) | 48.4 (30.0, 66.7) | 48.2 (29.9, 66.4) |
| *Muscle thickness (cm)* | | | | |
| Left elbow flexor* | 3.3 (2.1, 4.4) | 3.6 (2.8, 4.4) | 3.8 (2.4, 5.3) | 4.3 (3.2, 5.4) |
| Right elbow flexor* | 3.0 (2.5, 3.6) | 3.5 (2.7, 4.3) | 3.0 (2.2, 3.7) | 3.6 (2.5, 4.6) |
| Left elbow extensor | 3.0 (1.8, 4.2) | 3.0 (2.0, 4.0) | 3.7 (2.1, 5.3) | 3.6 (2.3, 4.9) |
| Right elbow extensor | 3.4 (2.4, 4.4) | 3.0 (2.6, 3.4) | 3.4 (2.1, 4.7) | 3.3 (2.8, 3.8) |
| Left knee flexor | 3.8 (2.6, 5.0) | 3.7 (1.9, 5.5) | 3.8 (2.4, 5.2) | 4.3 (2.2, 6.3) |
| Right knee flexor | 3.7 (2.5, 4.9) | 3.7 (2.9, 4.6) | 4.2 (2.8, 5.6) | 4.2 (3.2, 5.2) |
| Left knee extensor | 3.6 (3.0, 4.3) | 3.6 (2.9, 4.4) | 3.5 (2.6, 4.3) | 3.4 (2.5, 4.4) |
| Right knee extensor | 3.5 (3.0, 4.1) | 4.0 (3.4, 4.6) | 3.2 (2.5, 4.0) | 3.4 (2.6, 4.2) |
| Left side | 14.5 (10.4, 18.5) | 14.8 (11.4, 19.1) | 14.9 (10.2, 19.6) | 16.4 (12.5, 20.4) |
| Right side* | 13.8 (10.7, 16.8) | 14.8 (12.3, 17.3) | 14.0 (10.5, 17.5) | 15.3 (12.4, 18.3) |
| Appendicular | 24.9 (16.3, 33.5) | 25.9 (17.5, 34.3) | 22.1 (11.0, 33.2) | 24.2 (13.3, 35.0) |

Upper body = left and right arms combined. Lower body = left and right legs combined. Appendicular: Elbow and knee flexor and extensor muscle groups combined. *Significant time main effect ($p$ < 0.05)

**Table 3.** Means (95% confidence intervals) at baseline and 10 weeks for measures of balance, cognition, anxiety and depression.

| | Creatine ($n$ = 5) | | Placebo ($n$ = 3) | |
|---|---|---|---|---|
| | Baseline | 10 weeks | Baseline | 10 weeks |
| BBS* | 54 (52, 55) | 56 (55, 56) | 52 (50, 54) | 55 (55, 56) |
| MoCa* | 24 (20, 27) | 26 (22, 30) | 25 (20, 29) | 26 (21, 31) |
| GAD-7 | 5 (1, 9) | 1 (0, 3) | 3 (-2, 8) | 1 (-1, 3) |
| CES-D* | 19 (13, 25) | 12 (8, 16) | 19 (11, 27) | 15 (10, 20) |

BBS: Berg balance scale; MoCa: Montreal cognitive assessment; GAD-7: Generalized anxiety disorder; CES-D: Centre for epidemiologic studies-depression scale. * Significant time main effect ($p$ < 0.05)

## DISCUSSION

This was the first study to investigate the effects of PRT and creatine supplementation in a small cohort of stroke survivors. Ten weeks of PRT was effective for increasing muscle strength, muscle thickness, balance and cognition and decreasing symptoms of depression. The combination of creatine supplementation and PRT increased walking performance over time compared to PRT and placebo. There were no adverse events reported in regards to PRT or supplementation. Creatine or placebo combined with PRT had no detrimental effect on any outcome measure.

Resistance training program design may be important for producing beneficial effects in stroke survivors (30). PRT leads to greater neuromuscular activation and gains in muscle strength compared to functional exercises (2). Muscle strength is a key determinant of functionality and a decrease in strength contributes to chronic disability following a stroke (21). Only a few studies have investigated the effects of PRT on measures of muscle strength after stroke. In older adults (> 60 years of age; time since stroke: ~ 36 months), 10-12 weeks of PRT (2 sets of 8 repetitions using 80% baseline and bi-weekly 1-RM for 5 lower-body exercises; 3 days/week) significantly increased measures of lower-body strength (41). Flansbjer et al. (26) showed that 10 weeks of PRT (2 sets of repetitions to volitional fatigue using 60-80% 1-RM for knee flexion and extension, 2 minutes rest between; 2 days/week) significantly improved measures of lower-body muscle strength in individuals who have had a stroke (40-70 years of age, ≥ 6 months since stroke). Furthermore, 12 weeks of lower-body PRT (3 sets of 8-10 repetitions using 70% baseline and bi-weekly 1-RM for leg press, knee extension and ankle plantar- and dorsi-flexion exercise; 3 days/week) improved measures of muscle strength in older adults (> 60 years of age; > 20 months since stroke) (47). Our results expand on these findings by showing that PRT, which included upper- and lower-body exercises, improved upper- and lower-body strength. These results are clinically relevant because upper- and lower-body strength is associated with the ability to perform activities of daily living such as walking, rising from a chair and bringing ones hand to their mouth in stroke patients (12). We also found that PRT improved measures of balance and cognition. Loss of balance during walking is very common following a stroke (3) and approximately 70% of these individuals report a fall within the first year after a stroke (9). There is evidence that falls increase the risk of fracture after a stroke, inevitably resulting in greater morbidity and mortality (29). Unfortunately, our study was too short in duration with

too small of a sample size to accurately assess the effects of PRT and/or creatine supplementation on falls and fractures. Approximately 75% of stroke survivors experience cognitive disabilities which reduces independence and the ability to perform activities of daily living. While no mechanisms were measured, there is evidence that exercise can increase cerebral perfusion and brain-derived neurotropic factor leading to greater learning and memory (10) which may help explain the positive results from PRT. Finally, we observed a reduction in symptoms of depression over time which agrees with the work of Ouellette et al. (47). Depression is very common in stroke survivors, with up to 25% of individuals experiencing some form of depression ≤ 1 year after stroke (32). Depression leads to social isolation and functional and physical impairments (51). PRT may therefore serve as an effective intervention for attenuating depression after stroke. In contrast to these positive effects, PRT had no significant effect on lean tissue or fat mass, muscle thickness of the elbow extensors and knee flexors and extensors, or anxiety. Our low sample size likely reduced our ability to detect small changes in these measures over time. Future research should determine the mechanistic effects of longer-term PRT (> 10 weeks) and whether PRT reduces the risk and prevalence of falls and fractures in large sample sizes of stroke survivors.

Stroke survivors who supplemented with creatine experienced a significant increase in 6-minute walk performance over time (Δ 39.2 ± 12.7 m; $p$ = 0.002) with no significant change for those on placebo (Δ 16.0 ± 10.5 m; $p$ = 0.120). The 6-minute walk test has been established to measure functional exercise capacity in disease state individuals (13). A recent systematic review involving 6 studies concluded that a change of 14.0-30.5 m is clinically important and distances ≥ 30.5 m indicates that a real change has occurred (13). Based on our findings, PRT and/or creatine supplementation may have clinical relevance for stroke survivors. It is important to highlight that the average age of the 5 participants in the creatine group was 51 years compared to 73 years for the 3 participants in the placebo group. While no muscle morphological or gait analysis assessments were performed, it is possible that the large age gap between group influenced performance in the 6-minute walk test.

From a statistical perspective, creatine provided no greater effects on measures of lean tissue or fat mass, strength, balance, cognition or symptoms of anxiety and depression. The lack of findings between creatine and placebo are likely related to our very small sample size and short duration of PRT and supplementation. We have previously shown that creatine supplementation (0.1 $g \cdot kg^{-1} \cdot d^{-1}$) during 6-weeks of resistance training augmented gains in muscle strength in young, healthy resistance-trained participants compared to placebo (42). These contrasting findings may be associated with methodological differences between studies, including participant characteristics (age, training and health status), training program duration, frequency and design, and creatine ingestion strategy. Further, it is important to note that the group who consumed creatine experienced a ~ 1.2 kg increase in lean tissue mass over time which aligns with an average increase (~ 1.2 kg) found in three meta-analyses involving creatine supplementation and resistance training in older adults (17, 22, 25, 28).

There were limitations to this study not previously mentioned. First, only one participant in the PLA group was able to provide food records during the first and final week of supplementation which prevented us from determining whether habitual dietary intake between groups influenced our results. Second, it was assumed that all participants in the CR group would respond to creatine supplementation. However, no measure of intramuscular creatine content was made to determine each participant's responsiveness to creatine supplementation. Finally, we did not use the International Classification of Functioning, Disability and Health assessment in our participants.

*Conclusion*: Ten weeks of PRT had some positive effects on measures of muscle strength and size, balance, cognition, and depression. The addition of creatine to PRT significantly improved walking performance. PRT and creatine supplementation resulted in no adverse effects. The generalizability of these preliminary findings are limited by a small sample size, large age range between participants, and lack of clinical and mechanistic assessments. Future research should determine the effects of creatine supplementation and progressive resistance training in a large cohort of stroke survivors of similar age with similar disease progression and rehabilitation status.

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