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The effect of creatine supplementation on muscle function in childhood myositis: A randomized, double-blind, placebo-controlled feasibility study

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Short Running Head

Creatine for Juvenile Dermatomyositis

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Abstract

Objectives: To evaluate the feasibility of studying creatine in juvenile dermatomyositis (JDM). Secondary objectives were to determine the effect of creatine on muscle function and metabolism, aerobic capacity, fatigue, physical activity and quality of life, as well as its safety.

Methods: We conducted a 6-month double-blind, randomized, multiple-baseline design; patients were assigned to creatine or placebo. Feasibility was assessed using attended study visits, completed study procedures, and adherence. Muscle function, aerobic capacity and muscle strength were assessed with standardized exercise tests. Muscle metabolism was assessed using a 31-Phosphorus Magnetic Resonance Spectroscopy protocol. Fatigue, physical activity and quality of life were assessed by questionnaires. Statistical significance was estimated using a randomization (permutation) test. Changes in outcome measures taken at baseline and end-of-study were calculated using paired t tests.

Results: Median (range) adherence to the study drug was 88.5% (20.5-95.5%) and the proportion of subjects with 80% adherence or higher was 76.9%. There were no missed study visits. There were no statistically significant changes in muscle function, strength, aerobic capacity, disease

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activity, fatigue, physical activity or quality of life while subjects were on creatine compared to placebo. There were statistically significant adaptations in muscle metabolism (e.g., decrease in change in muscle pH following exercise, and decrease in Phosphate/Phosphocreatine ratio) at the end-of-study, compared to baseline. There were no significant adverse effects.

Conclusions: Creatine supplementation in children with JDM is feasible to study, and is safe and well-tolerated; it may lead to improvements in muscle metabolism.

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Introduction

Juvenile dermatomyositis (JDM) is a rare disease characterized by capillary vasculopathy, which it thought to lead to local hypoxia and atrophy; in muscles this results in decreased function and persistent weakness (1).

Treatment reduces inflammation and muscle damage, but muscle atrophy and weakness remain in many patients, even when JDM is inactive. Additionally, muscle strength, power output, and other measures of physical function are reduced, compared to healthy peers. For example, Hicks and colleagues have shown that affected children have reduced aerobic (VO_2) and work capacities (peak power, heart rate and anaerobic threshold), compared to healthy controls (2). Takken and colleagues have shown a 29% lower mean power output and a 28% lower peak power on a Wingate Anaerobic Test compared to healthy controls (3), and a 40% lower peak VO_2, and shorter mean exercise time on a treadmill test, compared to age and sex reference norms (4).

Reduced muscle function may be due to residual damage, corticosteroid damage, and deconditioning from reduced participation in physical activities (5, 6).

Additionally, disordered muscle energetics may contribute to the reduced muscle function in JDM. Several factors have been proposed, such as a reduction in oxidative capacity, and a reduction in key enzymes required for adenosine tri-phosphate (ATP) production (7-9). Decreases in the amount of phosphocreatine (PCr) in addition to ATP have been reported in children with JDM at rest, following exercise, and after recovery (10). Increases in the ratio of phosphate (Pi) to PCr (Pi/PCr) and the amount of adenosine diphosphate produced in children with JDM post-exercise suggest a decreased potential to either use, or supply, ATP or PCr (10). This, combined with a reduced muscular economy (i.e., a larger

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energy cost per unit of work and a higher reliance on anaerobic glycolysis for energy supplies (7)) could account for some of the weakness and fatigue experienced by these children.

Supplementation with creatine is a potential strategy to target these metabolic and muscle strength deficiencies. In patient populations such as these, where metabolic and energy deficiencies exist, creatine supplementation alone has been shown to be effective, potentially resulting in increased energy transfer between mitochondrial and cytosolic components of muscle cells via increased intramuscular creatine, PCr, and total creatine content (9, 11, 12).

Creatine supplementation is a safe, effective therapy for adults with muscular dystrophy and inflammatory myopathies. A recent meta-analysis showed that creatine supplementation, compared to placebo, improved muscle strength, functional tasks and activities of daily living in these patients (9). A separate trial showed that patients with metabolic myopathies benefit from creatine supplementation, showing improvements in grip strength and anaerobic function (13). This suggests that patients with a variety of muscular dystrophies and inflammatory myopathies may benefit from creatine supplementation.

There have only been two trials looking at creatine supplementation in myositis, with mixed results. A study in adults with dermato/polymyositis showed that a 6-month course of creatine supplementation results in a significant increase in muscle PCr/nucleoside triphosphate ratios (measured by magnetic resonance imaging and spectroscopy) and a reduction in time to complete functional tasks compared to placebo (8). Conversely, a randomized crossover trial in children with JDM using 12 weeks of creatine supplementation did not find evidence for improvements in intramuscular PCr concentration, muscle function, or clinical parameters of JDM, compared to placebo (14).

Given the conflicting results of previous studies in myositis, we conducted a creatine supplementation study in children with JDM. Our primary objective was to evaluate the feasibility of

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studying creatine supplementation, in a definitive clinical trial, in children with JDM, and its safety and tolerability. Our secondary objectives were to determine the effect of creatine supplementation on muscle function, disease activity, muscle metabolism, aerobic capacity, muscle strength, fatigue, physical activity and quality of life, when compared to placebo.

Materials and Methods

We conducted a 6-month clinical trial between May 2015 and May 2017 at The Hospital for Sick Children (SickKids) in Toronto, Canada. The trial is registered at clinicaltrials.gov (NCT02267005).

We used a double-blind, randomized, multiple-baseline design to assign patients to receive creatine or placebo. Multiple-baseline designs are useful when the sample population is small (as is the case for JDM), and to allow all subjects to be exposed to the intervention (15). Each patient randomly started creatine at one of 6 potential start times and was on creatine for a minimum of 4 weeks (maximum of 6 months), in order to achieve steady-state conditions. This is in line with previous work that shows that maintenance levels of muscle PCr concentration is achieved within days using both high dosing (20g/day) for 5-7 days or moderate dosing (3g/day) for 28 days (16-18).

Patients aged 7-18 years were recruited from the JDM clinic at SickKids if they met the following inclusion criteria: diagnosis of probable or definite JDM with onset age < 16 according to Bohan and Peter criteria (19), on a stable course of medication unlikely to change over the study period, and a minimum height of 132.5cm (to be able to use all the exercise testing equipment).

Patients were excluded if they were newly diagnosed (within 6 months), were unable to cooperate with, or too weak to participate in, study procedures, had impaired kidney function as determined by screening lab values, or were pregnant or planning to become pregnant within the study period.

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The study was approved by the institutional Research Ethics Board (Protocol Number: 1000041466); participants and/or their parents or guardians gave written informed consent.

The subjects were prescribed creatine/placebo based on their weight, up to 40kg, or their body surface area for those weighing >40kg at a dose of 150mg/kg/day or 4.69g/m^2/day, in chewable, lemon-flavoured tablets for 6 months (AlzChem, Trostburg, Germany). This dose is within the range shown effective in improving muscle function in RCTs of children with neuromuscular disorders in which no adverse side-effects were reported (20, 21).

The length of time of active creatine supplementation was randomized according to a pre-determined randomization table, generated using an online random number generator (random.org), which ensured that at least 1 subject would start creatine at every possible time point, and that not more than 50% of subjects would start at any one time point. Both types of tablets looked and tasted identical. Allocation was hidden; only the study pharmacist had access to the randomization table to preserve blinding.

Subjects completed 7 assessments, each 4 weeks apart. Study visits comprised a series of exercise tests, collection of descriptive measures, a clinical assessment, and some questionnaires.

We assessed feasibility using a combination of recruitment rate, attended vs missed study visits, proportion of completed study procedures, and adherence. The proportion of data that could be analyzed was also considered when assessing overall feasibility.

Details of all outcome assessments are in Supplementary Appendix A. To measure muscle function, we used the Wingate Anaerobic Test at every study visit (4, 7, 22-29). At baseline and end-of-study visits, we used the YMCA cycle ergometer submaximal test to measure aerobic capacity (30-32) and 31-Phosphorus Magnetic Resonance Spectroscopy (^{31}P-MRS) to measure muscle metabolism (10).

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At every study visit, we measured disease activity using the International Myositis Assessment and Clinical Studies (IMACS) group core set at every study visit (33), and we did a maximal jump test and a handgrip strength test (34-36).

We measured fatigue using the Pediatric Quality of Life (PedsQL) Fatigue Module (37), and both overall, and health-related quality of life using the Quality of My Life (QoML) scale (38). We measured treatment satisfaction using the Treatment Satisfaction Questionnaire for Medication (TSQM II) (39, 40). The three-day physical activity recall questionnaire (3DPAR) was used to estimate habitual physical activity levels (41). Anthropometric measurements (height, weight, waist circumference, and body fat percentage by skin fold caliper) were taken at baseline and end-of-study.

To measure adherence, we counted the amount of medication remaining at each study visit. To encourage adherence, a study coordinator maintained weekly contact with each participant with reminders to take the supplements, and to encourage the subjects to keep a medication diary. Good adherence was determined by the proportion of subjects that took 80% or more of their study medication tablets.

To determine tolerance and safety, we monitored side effects/adverse events at each visit. Laboratory measures of renal function (serum creatinine, urea and urine) were done at each visit. Additionally, measures of muscle damage, commonly monitored in JDM, including creatine kinase, lactate dehydrogenase , and aspartate aminotransferase were also done at each visit. Safety data was reviewed by an independent Data Safety Monitoring Committee at regular intervals.

Our primary outcome was the feasibility of studying creatine supplementation, and safety and tolerability. Our secondary outcomes were muscle function, disease activity, aerobic capacity, muscle metabolism, muscle strength, fatigue, physical activity, and quality of life.

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Changes in repeatedly measured outcomes were calculated by regressing outcome onto the differences in means between conditions (placebo or creatine, lagged by 1 month) using ordinary least squares to derive a regression coefficient for condition. The p-values were estimated through a randomization test. Changes in outcome measures taken at baseline and end-of-study were assessed using paired t tests.

We determined our sample size based on the number of subjects required to see a large effect size (ES = 2) with almost 90% power, assuming an intraclass correlation of 0.9 (to account for within-subject correlation, assuming an exchangeable correlation structure (42)), and a reasonable power to see moderate effect sizes, given the 6 possible start times for creatine.

We conducted all analyses using R v3.5.0.[1]

Results

Thirty-eight recruitment letters were mailed to eligible patients, and 20 patients (53%) expressed interest in the study. Thirteen subjects were enrolled between March 10, 2015 and December 6, 2016, with follow-up completed in May 2017 (Figure 1). Table 1 describes the clinical characteristics of our cohort. All 13 subjects remained on stable treatment during the study.

There were no serious adverse events. All laboratory values remained within normal ranges with the exception of one subject, who experienced some mild transient dehydration, as measured by elevated serum creatinine levels, which may have been attributable to creatine. With rehydration, the subject's creatinine levels returned to normal in subsequent laboratory evaluations, and there were no other signs of renal failure or muscle breakdown. The DSMC reviewed the results and indicated that no

[1] R Core Team (2018). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria

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further investigations were required. There were no other side effects or adverse events related to creatine.

Satisfaction with creatine was high, with a median (range of values, ROV) global satisfaction rating on the TSQM II of 83.3 (54.2-100.0). Median (ROV) adherence to the study drug was 88.5% (20.5-95.5%). The proportion of subjects with good adherence was 10/13 (76.9%).

There were no missed visits. We were able to complete 89/91 (97.8%) Wingate tests. One subject was unable to complete the baseline Wingate since her feet were unable to reach the pedals, and one subject was too exhausted during a single study visit to finish it.

There were some logistical issues with the MRI machines at SickKids; the Siemens 3T Tim Trio was decommissioned partway through the study. We attempted to schedule baseline visits for patients that would be affected with enough time for the MRI to be replaced so they could have their end-of-study scan on the new Siemens PRISMA 3T machine. However, the construction was delayed, resulting in several patients having their scans on different machines. Despite these challenges, all patients were able to complete both the baseline and end-of-study ^{31}P-MRS protocols.

Of the battery of physical assessments, only the YMCA cycle ergometer submaximal test posed some challenges. Several subjects were unable to complete the minimum work required to calculate peak VO_2 – 2 at baseline, 1 at end-of-study, and 2 at both baseline and end-of-study; data is available for 21/26 (80.8%) of possible tests.

There were no statistically significant changes in muscle function, muscle strength or aerobic capacity. We saw an increase of 9.5 watts in the peak power as measured on the Wingate, which failed to reach statistical significance (Table 2).

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There were no statistically significant changes in disease activity, quality of life, functional status as measured on the CHAQ, physical activity, time spent engaging in moderate to vigorous or vigorous activities, or fatigue (Table 2).

For the ^{31}P-MRS investigation, we were able to get usable data from only 8/13 (61.5%) subjects, even though all 13 completed the scans (due to change of machine – see above). We report the 8 subjects who had both baseline and end-of-study testing done in the Siemens 3T Tim Trio MRI and spectroscopy system.

^{31}P-MRS variables were assessed at rest, and the results were analyzed as the average of 20 resting spectra collected sequentially. There were no measurable differences in resting levels of Pi, Pi/PCr, adenosine triphosphate (ATP) or pH between baseline and end-of-study. However, there was a small (not statistically significant) increase in the amount of resting PCr (Table 3).

^{31}P-MRS variables were collected during recovery after the 30, 60, and 5x30-second exercise bouts (Table 4). There was a significant reduction in the Pi/PCr ratio following the 60 second bout and a dampened decrease in pH following the 5x30 second bouts at the end-of-study, compared to baseline.. There was less oxidative ATP produced following the 30 second exercise bout, and less anaerobic ATP and total ATP produced following the 5x30 second bouts at end-of-study compared to baseline ATP production rates.

Of importance, there was no difference between the mean (SD) workloads performed by the patients at baseline and end-of-study in each of the 30 second [baseline: 6.8 (2.4) W, end-of-study: 7.5 (2.3) W], 60 second [baseline: 5.9 (2.3) W, end-of-study: 6.6 (1.7) W], and 5x30 second [baseline: 4.7 (1.2) W, end-of-study: 4.8 (1.4) W] exercise bouts (p=0.06, 0.10 and 0.81 respectively).

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Discussion

Creatine supplementation appears to be well-tolerated and free of serious adverse effects in children with JDM. Most of the study procedures were feasible, suggesting that future studies using this design are highly likely to succeed. We also demonstrate that it is important to ensure compatible MRS techniques during longitudinal studies, as much of our data was not usable in this analysis due to MRI machine differences. While we did not see any statistically significant therapeutic effect in physical function, aerobic capacity, disease activity, fatigue, physical activity or quality of life, we did see improvement in muscle metabolism as evidenced by ^{31}P-MRS exercise testing.

We have shown that the study of creatine supplementation is feasible in JDM. The visit attendance, adherence, patient satisfaction, and our ability to collect the outcome measures were all very high. We believe that this patient population may have an appetite for continued improvement beyond the traditional treatment course for JDM and seem to be open to lifestyle interventions as an adjunct to medications.

We speculate that there are several reasons why we were able to show an improvement in muscle metabolism that did not translate to a clinically observable improvement. Our study was powered to detect a large effect size, so it is likely that small/moderate but clinically important effects would be missed, given our small sample size. It is also likely that since the outcome measures selected, such as the CHAQ, CMAS and MMT, were bounded by ceiling effects (43), these outcomes may have been ill suited to show improvement in this particular cohort with already relatively high functional status. These outcome measures were selected because they are part of the standard of care in our JDM clinic at SickKids. It is certainly possible that other measures that are not limited by ceiling effects – such as the Patient Reported Outcome Measures Information System (PROMIS) – may have demonstrated

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clinical improvement (44). Additionally, we did not include a specific exercise protocol in this study; our aim was to investigate creatine supplementation in isolation. Given the results of the study in adult myositis (8), we may have shown more clinical improvement if we had incorporated additional fitness/exercise into our protocol.

With regards to some of the patients' inability to complete the aerobic function test, we suspect that this is because many of our patients were deconditioned; this could be a result of many factors including disease or medication side effects (e.g., corticosteroid use), or decreased participation in physical activity (5, 6). It is also possible that patients' muscles had not yet recovered from completing the strenuous ^{31}P-MRS protocol earlier on the same day. However, we did not expect supplementation with creatine, in the absence of regular training, to improve aerobic capacity.

The increase in ATP production via aerobic oxidative phosphorylation in muscle mitochondria (Table 4) during the post-exercise recovery phase indicates improved aerobic oxidative contribution to the post exercise recovery associated with supplementation. There was a non-statistically significant increase in the amount of resting PCr at end of study compared to baseline, and a non-statistically significant decrease in Pi/PCr ratio immediately post-exercise. This suggests less metabolic stress at a given workload due to supplementation, however no statistically significant difference in resting PCr and Pi/PCr ratio may indicate that our sample size was too small, or that the subjects did not get enough creatine – because either the dose was insufficient, or adherence was limited.

The significant decrease in Pi/PCr ratio immediately post-exercise (60-second bout) indicates less metabolic stress at a given workload due to supplementation.

The results of the ^{31}P-MRS testing from the 5x30 seconds moderate intensity exercise were more revealing. After supplementation, there was a significant decrease in the change in pH between pre- and post-exercise. When the participants exercised, anaerobic glycolytic metabolism was activated

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resulting in lactic acid production, which immediately dissociates into a lactate molecule and an H^+ ion. The change in pH reflects the intra-muscular acid-base status of the muscle tissue. A lower amount of mean and maximal change in pH pre- vs post-exercise is indicative of lower anaerobic glycolytic metabolic stress after supplementation. These markers are supported by an observed significantly decreased ATP production rate (through creatine kinase and anaerobic glycolytic pathways) and decreased total ATP production rate. It is of note that there was a non-statistically-significant increased tau of the recovery rate of phosphocreatine between exercise bouts; there is a possibility of a type II error given our sample size.

We propose that the following observations are indicative of a lower metabolic stress post-intervention compared to pre-intervention: 1) a decrease in post-exercise Pi/PCr ratio, 2) less change in pH from pre- to post-exercise, and 3) a decreased total ATP production during the 5x30 second test. A lower Pi/PCr ratio suggests a smaller accumulation of Pi during exercise, and a decreased change in pH suggests less anaerobic metabolism required to complete the exercise (less accumulation of hydrogen ions from lactic acid production). Lower anaerobic and total ATP production suggest that there was a decreased reliance on anaerobic metabolism to complete the exercise. Taken together, these findings suggest an increased resting supply of stored energy in the form of PCr and/or greater efficiency of the aerobic oxidative energy system.

We observed an increase in the ATP produced via aerobic oxidation during the recovery period after 30 seconds of intense exercise, possibly due to a higher level of readily available PCr in the participants' muscle cells post-supplementation.

The lower ATP production via anaerobic pathways from the 5x30 second exercise test is also suggestive of a lower metabolic stress level following supplementation. Since the work done per unit of

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time during the exercise sessions did not differ between pre- and post-supplementation conditions, the lower ATP production rate post-supplementation can be interpreted as an improvement.

Taken together, these findings are intriguing and may be indicative of a signal that creatine supplementation improves bioenergetics metabolism in children with JDM; more definitive trials are needed to corroborate these results.

Our results must be interpreted considering several possible limitations. Supplementation with creatine may be more effective in conjunction with an exercise program (8). Therefore, it is possible that further improvements could have been elicited with simultaneous exercise training. We did not include an exercise training program in this study to allow us to investigate the effects of creatine supplementation in isolation, as this approach has been successful for other muscular dystrophies and inflammatory myopathies. However, given that all of the patients enrolled were relatively strong and functional at baseline, the capacity for clinical improvement based on creatine supplementation alone was likely very small.

Additionally, throughout the study, we calculated adherence using only drug returns to the pharmacy. We relied on our study subjects to be honest and return all unconsumed tablets. In future studies, a more accurate strategy might be to test urine for creatine levels.

Finally, we were unable to analyze the MRS changes for several of our subjects due to scanner incompatibility. Given the nature of the missing data (unrelated to patient characteristics/outcomes), this data is likely “missing completely at random”; complete data would most likely have given us higher precision rather than changed our conclusions.

We have shown that creatine supplementation in children with JDM is a feasible, safe and well-tolerated intervention and may, indeed, lead to improvements in muscle metabolism.

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TABLE 1 Baseline demographics and clinical characteristics of enrolled participants. All values are median (range of values) unless otherwise indicated.

	Participants (n=13)
Female (n)	7 (53.8%)
Age, years	13.0 (7.0-14.0)
Weight, kg	41.7 (25.6-64.6)
Body mass index, kg/m^2	18.2 (14.3-22.9)
Age at diagnosis, years	7.5 (2.5-12.0)
Race or ethnic group (n)	
White European	10 (76.9%)
Arab	1 (7.7%)
Mixed African Heritage/White European	1 (7.7%)
Mixed Chinese/Filipino	1 (7.7%)
Medications* (n)	
None	2 (15.4%)
Methotrexate	8 (61.5%)
Calcium/Vitamin D/Folic acid	8 (61.5%)
IVIG	3 (23.1%)
Other	3 (23.1%)
CMAS (0-52)	52 (46-52)
MMT-8 (0-80)	79 (60-80)
Physician Global Assessment (0-10)	0 (0-2.6)
3-Day Physical Activity Recall	
Total Metabolic Equivalents (METs)	66.3 (54.3-79.0)
Hours of Moderate to Vigorous Physical Activity (MVPA)	1.67 (0.5-3.67)
Hours of Vigorous Physical Activity (VPA)	1.0 (0-1.5)
*sum > 13 as subjects could be on more than 1 medication	

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TABLE 2 Mean differences in key outcome measures between while subjects were on creatine compared to on placebo.

Variable	**Mean difference**	**p-value**
Peak power (watts)	9.5	0.77
Fatigue Index (%)	1.09	0.77
Total Metabolic Equivalents (METs)	-1.24	1
Moderate-Vigorous physical activity (MVPA, number of 30 minute blocks)	0.11	0.87
Vigorous physical activity (VPA, number of 30 minute blocks)	-0.57	0.16
Childhood Health Assessment Questionnaire (CHAQ, /3)	0.005	0.81
Illness Rating (/100)	-2.60	0.235
Pain Rating (/100)	-0.26	0.929
Pediatric Quality of Life Fatigue Index (/100)	3.6	0.982
Right hand grip (kg)	-0.26	0.91
Left hand grip (kg)	-0.90	0.62
Max jump (inches)	-0.21	0.82
Physician global assessment (/100)	1.31	0.64
Patient global assessment (/100)	-0.56	0.89
Manual Muscle Testing (MMT8, /80)	0.81	0.59
CMAS (/52)	-0.08	0.88
Muscle disease activity (/100)	-0.25	0.78
Global disease activity (/100)	1.24	0.69
Overall Quality of My Life (/100)	3.03	0.64
Health related quality of life (/100)	1.60	0.13
YMCA-estimated peak VO_2	0.84	0.374
Body fat (%)	0.01	0.99
Waist circumference (cm)	1.51	0.05

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TABLE 3 ^{31}P-MRS testing results at rest. While none of the variables had changes that were statistically significant, there was a weak signal toward an increase in PCr at rest at the end-of-study.

Variable	Baseline (mean ± SD)	End-of-study (mean ± SD)	p-value
Resting PCr	18.86 ± 0.62	19.23 ± 0.68	0.12
Resting Pi	1.93 ± 0.20	1.82 ± 0.17	0.21
Resting ATP	20.51 ± 0.63	20.25 ± 0.67	0.21
Resting pH	6.96 ± 0.02	6.96 ± 0.02	0.33
Resting Pi/PCr (ratio)	0.10 ± 0.01	0.09 ± 0.01	0.16

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TABLE 4 ^{31}P-MRS exercise testing results at baseline (B) and end-of-study (E) for each of the three exercise tests: 30 seconds at maximal intensity, 60 seconds at moderate intensity, and 5x30 seconds at moderate intensity each separated by 15 seconds of rest.

Variable	Time Point	30 s test (mean ± SD)	p-value	60 s test (mean ± SD)	p-value	5 x 30 s test (mean ± SD)	p-value
Change in pH after exercise (rest pH-end exercise pH)	B	0.32 ± 0.28	0.57	0.46 ± 0.26	0.96	0.30 ± 0.27	0.003
	E	0.37 ± 0.43		0.45 ± 0.30		0.25 ± 0.26	
Pi/PCr (ratio)	B	1.30 ± 0.61	0.11	2.44 ± 1.20	0.03	2.48 ± 1.58	0.28
	E	1.17 ± 0.70		2.08 ± 1.12		2.33 ± 1.99	
ATP produced via creatine kinase (mmol·L·min^{-1})	B	0.31 ± 0.10	0.08	0.20 ± 0.04	0.25	0.34 ± 0.11	0.11
	E	0.29 ± 0.12		0.19 ± 0.06		0.31 ± 0.13	
ATP produced via anaerobic glycolysis (mmol·L·min^{-1})	B	0.69 ± 0.53	0.59	0.57 ± 0.33	0.23	0.92 ± 0.70	0.01
	E	0.65 ± 0.53		0.52 ± 0.33		0.80 ± 0.69	
ATP produced via aerobic oxidation (mmol·L·min^{-1})	B	0.30 ± 0.07	0.04	0.34 ± 0.14	0.24	0.23 ± 0.07	0.69
	E	0.23 ± 0.11		0.31 ± 0.16		0.21 ± 0.08	
ATP total produced via all pathways (mmol·L·min^{-1})	B	1.30 ± 0.64	0.13	1.11 ± 0.41	0.10	1.48 ± 0.82	0.02
	E	1.17 ± 0.75		1.02 ± 0.48		1.33 ± 0.84	

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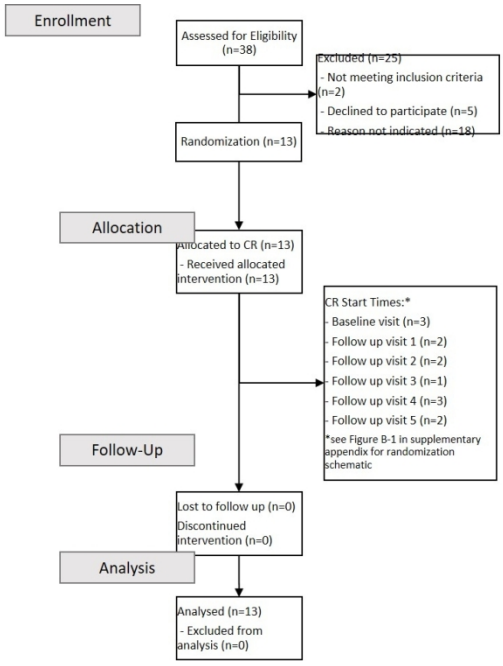

Patient flow diagram for multiple baseline design (CR = creatine)

245x161mm (150 x 150 DPI)

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