Effects of resistance exercise and creatine supplementation on myasthenia gravis: a case study

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ABSTRACT


Purpose: The purpose of this case study was to determine the effects of 15 wk of resistance exercise and creatine (Cr) supplementation on body composition, training volume, peak strength, and complete blood chemistry in a patient with myasthenia gravis (MG). Methods: The patient was a 26-yr-old man who was taking prednisone and azathioprine for his condition. The patient self-administered 5 g of Cr per day in addition to resistance exercise 3 times per week. Fasting blood samples were obtained and body weight (BW) and fat free mass (FFM: via hydrostatic weighing) were measured before and after training and Cr supplementation. In addition, isokinetic (Cybex II) peak strength for leg extension (LE), leg flexion (LF), and volume load (repetition × mass lifted) for the first and last resistance training session were determined. Results: After Cr supplementation and training, the results demonstrated increases in BW (6.8%), FFM (4.3%), upper body volume load (37.0%), lower body volume load (15.0%), and peak strength for LE (37.0%) and LF (12.5%). Moreover, blood chemistry values remained within normal limits for the duration of the 15-wk study. Conclusion: These data suggest that resistance exercise plus Cr supplementation may promote gains in strength and FFM in patients with MG. Key Words: NEUROMUSCULAR DISEASE, WEIGHT-TRAINING, ERGOCENIC AID

In skeletal muscle, creatine (Cr) is primarily stored as free Cr and phosphocreatine (PC) and is found naturally in foods such as meat. Phosphocreatine is the primary fuel reserve for the resynthesis of adenosine triphosphate during anaerobic exercise (18). Therefore, rapid depletion of muscle PC is believed to be a limiting factor when performing maximal anaerobic work (12,14). In healthy subjects, several studies have demonstrated ergogenic benefits from acute Cr supplementation on strength, running, cycling, and jumping (1,4,21,22,27). Furthermore, recent studies have also demonstrated that Cr supplementation during resistance training resulted in greater increases in fat-free mass (FFM), muscular-strength, and training volume load when compared with resistance training alone (2,15,23). Possible mechanisms responsible for the ergogenic effects of Cr supplementation include increased skeletal muscle PC content, improved energy shuttling, and/or enhanced skeletal muscle protein synthesis (3,13,27).

Within the last several years, Cr supplementation has been explored as a therapeutic intervention for various neuromuscular and neurodegenerative disorders (24–27), since skeletal muscle PC concentrations have been shown to be low in many of these conditions (16,26). Recently, Tarnopolsky and Martin (24) demonstrated that acute (10 d) Cr supplementation significantly increased strength and total body mass in patients with a variety of neuromuscular diseases, including mitochondrial cytopathies, dystrophies/congenital myopathies, and polymyositis.

Patients with myasthenia gravis (MG) typically exhibit skeletal muscle wasting, neuromuscular fatigue, and weakness (9). These symptoms are believed to be caused by a functional blocking or loss of postsynaptic acetylcholine receptors at the neuromuscular junction (7), as well as a decreased PC content in skeletal muscle (16). To date, no research has investigated the effects of resistance exercise with Cr supplementation in patients with MG. Therefore, the purpose of this case study was to determine the effects of 15 wk of resistance exercise and Cr supplementation on...
CASE HISTORY

E.M. is a 26-yr-old medical student who was diagnosed with MG in May 1995. Before the onset of the disease, he was a full-time college student, played college baseball, and was an avid weightlifter and runner. For 3 months before diagnosis, he noticed that he was becoming gradually weaker during weight training and experienced a slight loss in body weight. One month before diagnosis, his maximum bench press strength was 130 kg. However, at diagnosis, he was unable to perform one push-up. He presented with symptoms of unilateral ptosis progressing to both eyes, diplopia, and muscle atrophy. At the time of diagnosis, he weighed approximately 85 kg and had 5–6% body fat (via skin-fold).

He began a regimen of Mestinon (60 mg·d⁻¹), Imuran (azathioprine; 150 mg·d⁻¹), and prednisone (60 mg·d⁻¹). After approximately 6 wk of medical treatment, his ocular symptoms were controlled. However, the extreme weakness and muscle atrophy persisted. He began to exercise again at low levels, which prevented further weakness; however, he was unable to regain his lost strength and muscle mass. He continued to train at very minimal levels until undergoing a thymectomy performed via sternotomy in September 1995. At 3 months postsurgery, he independently began lifting weights and exercising aerobically. Despite dedicated training, he was unable to improve his strength and muscle mass above his postdiagnosis baseline. Pressing exercises involving the chest and triceps appeared to be most affected, and these muscle groups showed the most evidence of atrophy (left > right).

Over the next 18 months, E.M. was stable and began tapering off medications. During this time, he continued to train regularly without gains in strength or mass. He had completely discontinued medication by the end of the summer in 1997. That fall, after the beginning of medical school, he began experiencing visual symptoms of ptosis and diplopia and was placed on a reduced pharmacotherapeutic regimen of prednisone (40 mg·d⁻¹) and Imuran (150 mg·d⁻¹). The symptoms were controlled after approximately 4 wk of medication, and his condition remained stable through the summer of 1998. During this time, he continued to train with only minor gains in strength and mass.

Beginning in the fall of 1998, E.M. began to notice a decrease in his strength and a gradual reduction in his body weight (BW), despite making no changes in his exercise regimen or diet. From September to December, he lost approximately 4.5 kg of FFM, which was most noticeable in his shoulders, chest, and neck. In late November 1998, he again experienced frequent diplopia. After consulting his neurologist in January 1999, computerized tomography, magnetic resonance imaging, and thallium imaging studies were ordered to investigate the etiology of the symptoms. A mass of tissue, believed to be thymic remnants, was noted in the mediastinum. Because evidence exists showing that the presence of residual thymic tissue could cause a recurrence or exacerbation of MG, the tissue was considered as a possible source of symptoms. As a result of these findings, E.M. elected to have a repeat sternotomy in April 1999. At the time of surgery, his BW had decreased from his usual 83.0 kg to 74.8 kg, with a noticeable loss of muscle mass and strength.

After surgery, E.M. was restricted from lifting weights for 3 months and continued his medication (prednisone 40 mg·d⁻¹, Imuran 150 mg·d⁻¹) regimen. During this time, he gradually continued to increase his aerobic activity level and was able to maintain his BW between 74.8 and 77.1 kg. In July 1999, E.M. resumed his resistance training program (one exercise per each major muscle group for 3–4 sets, 3 times per week) and began to self-administer 5 g of Cr (FSI Nutrition, Omaha NE; U.S. Patent No. 5,925,378) per day for 15 wk.

METHODS

Before any measurements, E.M. and his physician signed an informed consent to participate in this case study. Body composition was assessed before and after Cr supplementation and training via underwater weighing (UWW) with correction for residual volume (RV) by using the oxygen dilution method of Wilmore (28). Residual volume was determined on land with the subject seated as in UWW. The average of similar scores (within 0.1 L) from two to three trials was used as the representative RV.

Underwater weight was measured in a submersion tank in which a seat was suspended from a Chatillon 9-kg scale. The average of the two to three highest weighings from 6 to 10 trials was used as the representative underwater weight. Percent body fat was calculated from body density (D₄ₒ) by using the revised formula of Brozek et al. (5), and fat free mass (FFM) was derived mathematically. In addition, a complete blood chemistry panel (Table 1) was obtained at weeks 0, 6, and 15.

Training volume (repetitions \times mass lifted) for upper body (dumbbell bench press, machine lat pulldown, dumbbell shoulder press) and lower body (leg extensions and leg curls) was monitored throughout the resistance-training program. In addition, maximal isokinetic leg flexion (LF) and leg extension (LE) strength of the dominant leg (based on kicking preference) was measured using a calibrated Cybex II dynamometer at 60°·s⁻¹ at baseline and postsupplementation (15 wk).

DISCUSSION

Recent investigations (10,11) using male subjects (age range = 19–60 yr) have shown that Cr loading (20 g·d⁻¹) for 5 d, or 3 g·d⁻¹ for 30 d, elevated whole-muscle Cr stores by an average of 20%, with as much as 20% stored in the form of PC. The male patient in this study was within the age range of those used in previous investigations and self-administered 5 g·d⁻¹ of Cr for 15 wk. Therefore, although muscle PC levels were not directly measured in the present

http://www.acsm-msse.org
TABLE 1. Blood chemistry values.

<table>
<thead>
<tr>
<th>Week</th>
<th>Week 0</th>
<th>Week 6</th>
<th>Week 15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood cell count</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WBC (10^3 μL)</td>
<td>8.8</td>
<td>5.1</td>
<td>4.6</td>
</tr>
<tr>
<td>RBC (10^6 μL)</td>
<td>4.46</td>
<td>4.53</td>
<td>4.54</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>13.8</td>
<td>13.8</td>
<td>13.9</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>40.5</td>
<td>40.1</td>
<td>41.2</td>
</tr>
<tr>
<td>MCV (μm³)</td>
<td>90.7</td>
<td>88.3</td>
<td>90.6</td>
</tr>
<tr>
<td>MCH (pg)</td>
<td>31.0</td>
<td>30.3</td>
<td>30.7</td>
</tr>
<tr>
<td>MCHC (g/DL)</td>
<td>34.1</td>
<td>34.3</td>
<td>33.9</td>
</tr>
<tr>
<td>RDW (%)</td>
<td>14.1</td>
<td>13.8</td>
<td>13.0</td>
</tr>
<tr>
<td>Platelet (10^3)</td>
<td>205</td>
<td>208</td>
<td>198</td>
</tr>
</tbody>
</table>

Differential

- Neutrophils, absolute (10^3) | 5.0 | 2.6 | 2.8 |
- Absolute lymph (10^3) | 3.2 | 2.1 | 1.5 |
- Monocytes, absolute (10^3) | 0.5 | 0.3 | 0.3 |
- Eosinophils, absolute (10^3) | 0.0 | 0.0 | 0.0 |
- Neutrophils (%) | 57 | 51 | 59 |
- Lymph (%) | 36 | 42 | 33 |
- Monocytes (%) | 7 | 7 | 6 |
- Eosinophils (%) | 0 | 1 | 1 |
- Basophils (%) | 0 | 0 | 1 |
- RBC size | Normal | Normal | Normal |
- RBC color | Normal | Normal | Normal |
- RBC shape | Normal | Normal | Normal |

General chemistry

- AST (IU/L) | 41 | 51 | 52 |
- ALT (IU/L) | 20 | 31 | 39 |
- Total bilirubin (mg/dL) | 0.9 | 0.6 | 0.9 |
- Direct bilirubin (mg/dL) | 0.2 | 0.1 | 0.1 |
- Albumin (g/dL) | 4.5 | 4.6 | 4.8 |

White blood cell (WBC); red blood cell (RBC); mean corpuscular volume (MCV); mean corpuscular hemoglobin (MCH); mean corpuscular hemoglobin concentration (MCHC); red cell distribution width (RDW); alkaline phosphatase (ALP); aspartate aminotransferase (AST); alanine aminotransferase (ALT).

study, the results of previous investigations (10,11) suggest that Cr supplementation likely resulted in an increase in muscle PC concentration.

Tarnopolsky and Martin (24) have previously demonstrated that acute (10-d) Cr supplementation significantly increased strength and total mass in patients with various neuromuscular diseases. The results of this case study indicated that 15 wk of Cr supplementation and resistance training increased BW (6.8%), FFM (4.3%), upper body volume load (37.0%), lower body volume load (15.0%), and peak strength for LE (37.0%) and LF (12.4%) (Table 2). These results are similar to previous studies using healthy male subjects, which reported increases in FFM ranging from 3.9% to 4.6%, as well as significant increases in upper and lower body strength after 4–8 wk of resistance training and Cr supplementation (8,15,23). As indicated in the case history, while in remission, E.M. was unable to make significant gains in strength or FFM as a result of his resistance exercise program, which may have been a consequence of his medication. Miller et al. (19) have demonstrated that MG patients orally receiving 40 mg·d⁻¹ to 100 mg·d⁻¹ of prednisone experienced a decrease in maximal voluntary strength. Although we cannot determine to what extent each intervention (creatine and exercise) contributed to changes in strength and body composition, it should be noted that during the entire 15 wk, E.M. was receiving 60 mg·d⁻¹ of prednisone. Although it could be speculated that creatine may attenuate the decline in neuromuscular function in MG patients receiving corticosteroids, future studies are warranted to validate this theory.

The possible mechanisms responsible for the effects of Cr supplementation on body composition and strength include: 1) a significant increase in Tc content, which would allow for a greater total training volume (8,27) and, consequently, a greater training stimulus; and/or 2) a Cr-driven increase in protein synthesis (3,13), possibly through enhanced satellite cell mitotic activity (6). The results of this case study support the hypotheses of Earnest et al. (8) and Voile et al. (27), who suggested that increasing PC stores in skeletal muscle through Cr supplementation during a resistance-training program may promote greater physiological adaptation over time when compared with training alone.

Recently, Kreider et al. (15) monitored the effects of Cr supplementation and resistance exercise for 28 d on complete blood chemistry responses (cell blood counts with percent differentials) in healthy male athletes. No adverse effects were reported and the hematological parameters remained within normal clinical limits (15). In the present study, we also monitored complete blood chemistry values for adverse reactions and possible exacerbation of reported side effects (hepatotoxicity, bone marrow depression and nausea) from E.M.’s medications (prednisone and azathioprine; Table 1). The blood chemistry values remained within normal limits throughout the 15 wk of supplementation and training, which is in agreement with the findings of Kreider et al. (15). Further, E.M. reported no gastrointestinal distress and/or any other medical problems. In addition, there was no report of skeletal-muscle cramping during resistance training sessions. It has been suggested that Cr supplementation may adversely affect kidney function; therefore, future studies should also measure serum creatinine levels and glomerular filtration rate.

Future double-blind research should be conducted to validate the effects of Cr supplementation and resistance training on a larger sample of patients with MG. Certainly, the use of a single subject was a limitation of this study. However, from a clinical viewpoint, healthcare practitioners must be cognizant that many patients self-administer physical activity and an array of over-the-counter supplements without knowledge of their side effects. Notably, the aggressive resistance exercise program implemented by this patient is in contrast to the

<table>
<thead>
<tr>
<th>Age</th>
<th>Sex</th>
<th>Weight (lbs)</th>
<th>Height (in)</th>
<th>Years</th>
<th>Muscle Composition</th>
<th>Training Volume</th>
<th>Peak Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>M</td>
<td>180</td>
<td>68</td>
<td>1.5</td>
<td>decrease</td>
<td>increase</td>
<td>increase</td>
</tr>
</tbody>
</table>
relatively conservative activity typically recommended for patients with MG (20). Furthermore, it is important that clinicians who treat or counsel these individuals become educated about the potential benefits (or detriments) of such substances and exercise programs. This expanded knowledge base may also better prepare clinicians to develop collaborative relationships with their patients, whereby patients can play an active role in devising their own treatment strategies under medical supervision, the advantages of which are substantial for adherence and outcomes (17).

In conclusion, the results of this study may lend support to previous investigations (15, 24–26) regarding the safety and the potential value of combining resistance exercise and Cr supplementation on strength and body composition in patients with various neuromuscular disorders, including MG. However, it should be noted that the increase in strength and FFM observed in this study may have been due to the strength training per se and the contribution from creatine is not measurable.

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REFERENCES


