Creatine Therapy in Myophosphorylase Deficiency (McArdle Disease)

A Placebo-Controlled Crossover Trial

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Objective: To determine whether treatment with creatine can improve exercise intolerance in myophosphorylase deficiency (McArdle disease).

Design: Double-blind, placebo-controlled crossover study with oral creatine monohydrate supplementation.

Patients: Nine patients with biochemically and genetically proven McArdle disease were treated.

Intervention: Five days of daily high-dose creatine intake (150 mg/kg body weight) were followed by daily low-dose creatine intake (60 mg/kg). Each treatment phase with creatine or placebo lasted 5 weeks.

Main Outcome Measures: The effect of treatment was estimated at the end of each treatment phase by recording clinical scores, ergometer exercise test results, phosphorus 31 nuclear magnetic resonance spectroscopy, and surface electromyography.

Results: Of 9 patients, 5 reported improvement of muscle complaints with creatine. Force-time integrals ($P = .03$) and depletion of phosphocreatine ($P = .04$) increased significantly during ischemic exercise with creatine. Phosphocreatine depletion also increased significantly during aerobic exercise ($P = .006$). The decrease of median frequency in surface electromyograms during contraction was significantly larger ($P = .03$) with creatine.

Conclusion: This is the first controlled study indicating that creatine supplementation improves skeletal muscle function in McArdle disease.

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McARDLE DISEASE is a rare autosomal recessive metabolic myopathy caused by a defect of the muscle-specific isozyme of glycogen phosphorylase that leads to a blockade of adenosine triphosphate (ATP) formation from glycogen in skeletal muscle. The defect in the glycogen breakdown pathway leads to deprivation of an important energy source, particularly during the early stages of exercise when the availability of fatty acids for oxidation is limited. Typically, patients with McArdle disease have exercise intolerance with premature fatigue, exercise-induced muscle pain in working muscles, and recurrent myoglobinuria, which usually start in childhood. Treatments for McArdle disease have been unsatisfactory.1

Creatine is a naturally occurring compound. Interconversion between creatine (Cr) and phosphocreatine (PCr) is catalyzed by creatine kinase: $\text{PCr} + \text{ADP} \leftrightarrow \text{ATP} + \text{Cr}$, where ADP indicates adenosine diphosphate. This reaction is near equilibrium in skeletal muscle and is important in buffering ATP against changing energy demand and in determining ADP, an important regulating factor in processes like oxidative phosphorylation.4 Net phosphocreatine hydrolysis provides ATP directly in the early stages of exercise.5 The intake of exogenous creatine, in doses of 10 to 20 g daily was well tolerated and resulted in an average increase of approximately 20% of total creatine and phosphocreatine in skeletal muscle.6 In healthy individuals and in patients with mitochondrial cytopathies, creatine supplementation improved exercise performance during repeated bouts of maximal-intensity exercise.7-13

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We hypothesized that creatine monohydrate supplementation for patients with McArdle disease would improve exercise intolerance and be well tolerated. To address this issue, we performed the present double-blind, placebo-controlled crossover trial in 9 patients with McArdle disease.
PATIENTS AND METHODS

PATIENTS

Nine patients (6 women, 3 men; mean ± SD age, 39.1 ± 17.9 years) with biochemically and genetically proven McArdle disease entered the trial. All patients had clinical features of exercise intolerance, defined as early fatigue and exercise-induced muscle pain in working muscle. Of the 9 patients, 3 (patients 1, 7, and 8) had fixed proximal weakness (Table 1). All patients led a normal life but were limited in daily activities, such as walking uphill and climbing stairs, and they could not carry out vigorous activities. Written informed consent was obtained from all patients after the study had been fully explained. The ethics committee of the University of Bochum, Bochum, Germany, approved the study protocol.

STUDY DESIGN

Patients were randomly assigned to receive either creatine capsules or placebo capsules. One group took creatine capsules, 150 mg/kg body weight daily for 1 week, followed by 60 mg/kg body weight daily (Figure 1). The other group took the same amount of an identical-looking placebo for the same period. Each treatment phase lasted 5 weeks. Both phases were separated by a 4-week washout period. The capsules contained either creatine monohydrate, 750 mg, or lactose (placebo), 750 mg, and were taken in 3 divided doses with major meals. Creatine and placebo capsules were generously provided by ViaNova (Waltenhofen, Germany). At the final day of each treatment period, clinical measurements and laboratory studies were performed first, followed by surface electromyography (S-EMG), ergometer exercise test, and finally phosphorus 31 nuclear magnetic resonance (NMR) spectroscopy.

CLINICAL RATING SCALES

The clinical rating scales were devised to describe the clinical symptoms of exercise intolerance. The fatigue severity scale (FSS) was administered to quantify early fatigue on exertion. Higher scores indicated worse performing, with a maximum score of 63 indicating worst functioning, and a score of 7 indicating normal performance. Severity of exercise-induced muscle pain in working muscles was graded using the following system: 0, none; 1, slight (painful, but no functional impairment); 2, moderate (painful, functionally impairing); and 3, severe (very painful, patient must rest). Each patient was asked to indicate the frequency (bouts) of muscle pain: 0, none; 1, sporadic (<1 bout per week); 2, frequent (2-7 bouts per week); and 3, very frequent (>7 bouts per week).

LABORATORY STUDIES

Blood samples were taken from an antecubital vein before and at the end of each treatment period. Creatine levels were determined colorimetrically using an enzymatic method.

ERGOMETER EXERCISE TEST

Ergometric tests were performed on an electrically braked bicycle ergometer. The test began with 6 minutes of rest while the subjects sat on the ergometer followed by exercising 3 minutes at a work rate of 23 W. Work rates were then increased every 3 minutes by 25 W. Exercise was continued until severe general or leg fatigue was prominent or until the submaximal heart rate of 200 − age (in years) was obtained. Maximal workload and maximal duration of ergometer exercise were measured.

PHOSPHORUS 31 NMR SPECTROSCOPY

Phosphorus 31 NMR spectroscopy, exercise protocol, and analysis of 31P-NMR data were identical to a previous report. The NMR spectra were obtained in a 4.7-T, 40-cm horizontal bore spectrometer (Bruker-Biospec 47/40; Bruker-Medizintechnik, Karlsruhe, Germany), using a 5-cm diameter surface coil placed under the right calf muscle. The patients were placed in the supine position with the upper body elevated by 25°. The foot was fixed on a pedal ergometer designed for isometric foot plantar flexion exercise. Arterial occlusion was induced using an air cuff placed around the lower part of the right thigh, which was rapidly inflated to 280 to 300 mm Hg using compressed air. Isometric maximum voluntary contraction (MVC) of foot plantar flexion was determined as the highest of 3 contractions.

Continued on next page
force-time integrals were calculated for the aerobic as well as ischemic exercise period and given in newton-minutes. Metabolite levels were expressed as percentage of phosphocreatine at initial rest. Absolute metabolite concentrations in millimoles per liter of cell water were calculated assuming that during the initial phase of rest, the value of ATP is 8.2 mmol/L.19 The concentration of ADP and the intracellular pH were determined as previously described.20-21 The time constants for phosphocreatine recovery were measured after aerobic (τ1) as well as ischemic (τ2) contraction. The changes of metabolite levels for phosphocreatine, ATP, and pH during the aerobic as well as ischemic exercise were calculated as differences of the values at the beginning of exercise minus those at the end of exercise. The changes of metabolite levels for ADP, phosphomonoester (PME), and inorganic phosphate (Pi) were measured as differences of the values at the end of exercise minus those at the beginning of exercise. Typical 31P-NMR spectra taken from a patient with McArdle disease are shown in Figure 3.

SURFACE ELECTROMYOGRAPHY

The S-EMG was derived from the right gastrocnemius muscle during isometric foot plantar flexion. The experimental setup was similar to that used for 31P-NMR. The patients performed a contraction of 30% MVC for about 2.5 minutes. The S-EMG was recorded by surface electrodes placed about 20 cm above the ankle joint over the gastrocnemius muscle in the direction of the muscle fibers. The raw EMG was recorded on an analog magnetic tape (bandwidth, 0 to 1.2 kHz) and evaluated offline. The signals underwent band-pass filtering between 3 and 500 Hz and analog-digital conversion with a sample rate of 1024 Hz. The time courses for the root mean square (RMS) as a measure of the EMG amplitude and for the median frequency (MF) characterizing the EMG spectral distribution were calculated as previously described.22,23 A typical S-EMG time course is shown in Figure 4.

STATISTICS

The analysis of all continuous parameters of interest (FSS, laboratory studies, ergometer exercise test, S-EMG, and 31P-NMR) was performed in a standard way for crossover trials, with 2-sample t tests for the intraindividual period differences, assuming no carryover effects and at most equal period effects (2-sided α=.05).24 For each parameter, we included the maximum number of patients available (9 for FSS, 8 for laboratory studies, and 7 for the ergometer exercise test, S-EMG, and 31P-NMR). For the clinical rating scores of muscle complaints, we performed the sign test on the intraindividual period differences (neglecting group membership and hence having to assume no period effects). All analyses were performed using SAS statistical software version 6.12 (SAS Institute Inc, Cary, NC).

Figure 1. Trial profile of a randomized, double-blind, placebo-controlled crossover trial of creatine therapy in patients with McArdle disease.

Figure 2. Exercise protocol of the phosphorus 31 nuclear magnetic resonance spectroscopy. MVC indicates maximum voluntary contraction.

Figure 3.
differences in maximum workload ($P = .68$) and in maximal duration of exercise ($P = .70$).

**$^{31}$P-NMR SPECTROSCOPY**

The $^{31}$P-NMR data were evaluated in 7 of the 9 patients. In patients 1 and 9, $^{31}$P-NMR could not be recorded; the patients could not fit in the spectrometer because they were overweight. For the mean levels of all measured values at initial rest, there was no significant difference with creatine use (phosphocreatine, $P = .15$; PME, $P = .87$; ADP, $P = .30$; Pi, $P = .76$; and pH, $P = .81$) (Table 3). Furthermore, creatine did not significantly alter the time courses of ATP ($P = .64$), ADP ($P = .33$), and pH ($P = .53$) values during aerobic exercise or the time courses of ATP ($P = .19$), ADP ($P = .11$), and pH ($P = .66$) values during ischemic exercise. The time constants of oxidative phosphocreatine recovery from aerobic ($P = .45$) and ischemic ($P = .60$) exercise also were not significantly different from those with placebo. However, during ischemic exercise, the force-time integral was significantly higher with creatine ($P = .03$). Consequently, phosphocreatine depletion ($P = .04$) and the accumulation of Pi ($P = .046$) increased during ischemic exercise with creatine. In addition, during aerobic exercise with creatine, a significant increase was observed in phosphocreatine depletion ($P = .006$) and a trend toward increase of Pi elevation ($P = .09$). The force-time integrals during aerobic exercise did not change significantly ($P = .22$) (Table 3). Force-time integrals varied considerably among the patients (Figure 5). Force-time integrals increased with creatine in 4 of the 7 patients during aerobic exercise and in 6 of the 7 patients during ischemic exercise. Phosphocreatine consumption increased in 5 of the 7 patients during ischemic as well as aerobic exercise with creatine. A concomitant elevation of Pi resulting from phosphocreatine breakdown was also measured in 5 patients during aerobic as well as ischemic exercise with creatine.

**SURFACE ELECTROMYOGRAPHY**

Surface electromyograms were evaluated for 7 of the 9 patients. For patients 7 and 8, data analysis was not possible because the signal intensities were too weak. For all patients and both treatment phases, a negative slope for MF was found, indicating a shift in the frequency spectrum to lower frequencies over time. For RMS, a positive slope was observed for all persons, with the exception of patient 1, in whom a small negative slope was found with placebo (Table 3). Thus, in almost all cases, a clear increase in the EMG amplitude was observed during sustained contraction. The individual differences for the slopes after ingesting creatine and placebo are shown in Table 3 and Figure 6. A uniform influence of creatine was established for MF; its decrease over time was steeper with creatine for all patients with the exception of patient 2. However, the influence of creatine on the RMS slope was nonuniform. Statistical analysis revealed a significant influence of creatine on the MF slope ($P = .03$).

**COMMENT**

This is the first direct investigation of the effects of creatine ingestion in patients with McArdle disease. Dietary creatine supplementation caused a substantial increase in the plasma concentration of creatine and was well tolerated. This is in agreement with previous studies showing that short-term and long-term oral creatine ingestion at a dosage up to 20 g/d causes no adverse ef-
Effects and significantly increases plasma creatine values.7-12 Muscle contraction, ion transport, and ATP hydrolysis are coupled by specific adenosine triphosphatases (ATPases); for example, myofibrillar, calcium (Ca²⁺), and sodium-potassium (Na⁺K⁺) ATPases. During exercise, the metabolic processes for continuous ATP resynthesis include oxidative phosphorylation, glycolysis, and the creatine kinase and myokinase (2ADP ⇔ AMP + ATP, where AMP indicates adenosine monophosphate) reactions. In McArdle disease, oxidative phosphorylation is limited by reduced substrate availability, and glycolysis is virtually absent, causing a severe limitation in the maximal rate of ATP resynthesis.23,20 Despite the limited capacity for ATP resynthesis, little or no decline in muscle ATP has been observed during fatiguing exercise in McArdle disease.27-30 Therefore, exercise intolerance cannot simply be explained by a lack of energy supply to the contractile mechanisms of muscle. Other factors, like alterations in the energy metabolism of membrane excitation and limitation of phosphocreatine breakdown, must be considered.23,28,31

Table 2. Clinical, Laboratory Study, and Ergometer Exercise Test Data for 9 Patients With McArdle Disease

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Patient 1</th>
<th>Patient 4</th>
<th>Patient 5</th>
<th>Patient 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>Creatine</td>
<td>Placebo</td>
<td>Creatine</td>
<td>Placebo</td>
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<tr>
<td>Fatigue severity scale16</td>
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<td>54</td>
<td>43</td>
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<tr>
<td>Muscle cramp scale</td>
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<td></td>
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<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Frequency</td>
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<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Laboratory studies</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatine kinase, U/L</td>
<td>361</td>
<td>785</td>
<td>8310</td>
<td>12630</td>
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<tr>
<td>Creatine, µmol/L</td>
<td>70.3</td>
<td>384.8</td>
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<td>297.7</td>
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<tr>
<td>Ergometer exercise test</td>
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<tr>
<td>Maximum workload, W</td>
<td>...</td>
<td>...</td>
<td>100</td>
<td>125</td>
</tr>
<tr>
<td>Maximum duration, min</td>
<td>...</td>
<td>...</td>
<td>11.3</td>
<td>12.5</td>
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</table>

*Group 1 (n = 4) received placebo as allocated in the first treatment phase and creatine in the second treatment phase. Group 2 (n = 5) received creatine as allocated in the first treatment phase and placebo in the second treatment phase. Ellipses indicate data not applicable; Δ, period differences between the first and second treatment phases.

Table 3. Data From Phosphorus 31 NMR Spectroscopy and S-EMG for 2 Treatment Phases for 9 Patients With McArdle Disease

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Patient 1</th>
<th>Patient 4</th>
<th>Patient 5</th>
<th>Patient 6</th>
</tr>
</thead>
<tbody>
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<td>Placebo</td>
<td>Creatine</td>
<td>Placebo</td>
</tr>
<tr>
<td>31P-NMR Values</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCr at initial rest, mmol/L</td>
<td>...</td>
<td>...</td>
<td>30.3</td>
<td>33.2</td>
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<tr>
<td>Pi at initial rest, mmol/L</td>
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<td>...</td>
<td>2.6</td>
<td>3.7</td>
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<tr>
<td>ATP at initial rest, mmol/L19</td>
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<td>...</td>
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<td>0.2</td>
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<td>PME at initial rest, mmol/L</td>
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<td>...</td>
<td>7.08</td>
<td>7.14</td>
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<tr>
<td>pH at initial rest</td>
<td>...</td>
<td>...</td>
<td>7.08</td>
<td>7.14</td>
</tr>
<tr>
<td>Force-time integral, N · min</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>During aerobic exercise</td>
<td>...</td>
<td>...</td>
<td>849</td>
<td>1012</td>
</tr>
<tr>
<td>During ischemic exercise</td>
<td>...</td>
<td>...</td>
<td>679</td>
<td>658</td>
</tr>
<tr>
<td>PCr consumption, mmol/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>During aerobic exercise</td>
<td>...</td>
<td>...</td>
<td>15</td>
<td>28.9</td>
</tr>
<tr>
<td>During ischemic exercise</td>
<td>...</td>
<td>...</td>
<td>21</td>
<td>29.8</td>
</tr>
<tr>
<td>Pi elevation, mmol/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>During aerobic exercise</td>
<td>...</td>
<td>...</td>
<td>16.2</td>
<td>28.9</td>
</tr>
<tr>
<td>During ischemic exercise</td>
<td>...</td>
<td>...</td>
<td>22.4</td>
<td>30.2</td>
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<tr>
<td>S-EMG Values</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RMS slope, %/min</td>
<td>−1.93</td>
<td>6.38</td>
<td>33.96</td>
<td>92.63</td>
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<tr>
<td>MF slope, Hz/min</td>
<td>−2.92</td>
<td>−7.58</td>
<td>−23.91</td>
<td>−25.15</td>
</tr>
</tbody>
</table>

*Group 1 (n = 4) received placebo as allocated in the first treatment phase and creatine as allocated in the first treatment phase and placebo in the second treatment phase. Ellipses indicate data not available; Δ, period differences between the first and second treatment phases; PCr, phosphocreatine; Pi, inorganic phosphate; ATP, adenosine triphosphate; ADP, adenosine diphosphate; PME, phosphomonoester; RMS, root mean square; and MF, median frequency.
To our knowledge, this study is the first to provide objective evidence that creatine supplementation improves exercise performance in McArdle disease, mainly during ischemic exercise. This is a combined effect of an increase in MVC and in the ability to maintain 30% MVC for a longer period before fatigue. This enhanced exercise performance is associated with increased intramuscular phosphocreatine use. The precise physiological mechanisms underlying this ergogenic action of creatine remain to be clarified. Although the blood concentration of creatine significantly increased with creatine supplementation, we could not demonstrate a significant increase in muscle phosphocreatine content. Therefore, the therapeutic changes of creatine are not mediated through elevated intramuscular phosphocreatine, but may involve other factors, like enhanced energy shuttling, stimulation of mitochondrial respiration, stabilization of mitochondrial creatine kinase, or improvements primarily at the neuronal system.32

The S-EMGs in this study are characterized by an increase in RMS and a decrease in MF over time. Such changes...
During Aerobic Exercise During Ischemic Exercise

Figure 5. Individual phosphorus 31 nuclear magnetic resonance spectroscopy values at the end of the creatine phase vs end of the placebo phase. Lines connect the values for a given subject. Average force-time integral, phosphocreatine (PCr) consumption, and inorganic phosphate (Pi) accumulation during ischemic exercise, and PCr consumption during aerobic exercise were significantly changed by creatine.

Figure 6. Individual surface electromyogram values at the end of the creatine phase vs end of the placebo phase. Lines connect the values for a given subject. In case of root mean square (RMS), the slopes are related to the RMS value at the beginning of the contraction period. The average slope for median frequency (MF) was significantly changed by creatine.
are typically found during-fatiguing muscle contractions. In normal subjects, an accumulation of potassium in the extracellular space has been regarded as the main reason for fatigue-induced changes in the EMG.33,34 In McArdle disease, this effect is enhanced, since NaK-ATPase is reduced35 and the blood potassium concentration during exercise significantly increased.35,36 Such an increase in the extracellular potassium concentration results in reduced excitability of the muscle fiber membrane as well as a decrease in the action potential amplitude.37-39 Accordingly, the force per action potential decreases.40 In this study, S-EMG revealed an enhanced time-related decrease in MF induced muscle pain in McArdle disease. These results point to a possible new symptomatic therapy in this glycogenolytic disorder. Further trials are needed to confirm this therapeutic effect. Accepted for publication August 6, 1999. We thank Richard Smolka from the Institute of Occupational Physiology, Dortmund, Germany, for his excellent technical assistance.

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