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# Effects of creatine supplementation on muscle weakness in patients with rheumatoid arthritis

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## Abstract

*Background and objectives.* Patients with rheumatoid arthritis (RA) frequently suffer from muscle weakness. Oral administration of creatine has been shown to improve muscle strength in healthy subjects. The objective of this study was to examine the effect of oral creatine supplementation on muscle weakness, disease activity and activities of daily living in patients with RA.

*Methods.* During a period of 3 weeks, 12 patients with RA were treated with creatine monohydrate (20 g/day for 5 days followed by 2 g/day for 16 days). They were examined on entry and at the end of the study. The patients were investigated clinically, blood and urine samples were obtained, muscle biopsies were performed before and after treatment, muscle strength was determined, and self-administered patient questionnaires were completed.

*Results.* From all patients we were able to obtain full clinical and questionnaire data, while biopsies were taken from 12 patients at the start and from nine patients at the end of the study. Muscle strength, as determined by the muscle strength index, increased in eight of 12 patients. In contrast, physical functional ability and disease activity did not change significantly. The creatine concentration in serum and skeletal muscle increased significantly, while creatine phosphate and total creatine did not increase in skeletal muscle. The skeletal muscle creatine content was associated with muscle strength at baseline but not after administration of creatine. The changes in muscle strength were not associated with the changes in skeletal muscle creatine or creatine phosphate.

*Conclusion.* Although the skeletal muscle creatine content and muscle strength increased with creatine administration in some patients with RA, a clear clinical benefit could not be demonstrated for this treatment when the patients were considered as one group.

KEY WORDS: Creatine kinase, Creatine supplementation, Muscle strength, Rheumatoid arthritis.

The importance of muscle weakness in the disability of patients with rheumatoid arthritis (RA) has long been recognized [1–5]. Muscle weakness is generally attributed to a reflex response to pain, joint deformation or disuse, extra-articular manifestations of the disease and/or psychological factors. In comparison, muscle inflammation with an increase in serum creatine kinase (CK) activity and specific histological changes are rare in patients with RA [6, 7].

More commonly, muscle weakness in RA is accompanied by normal or low serum CK activity, lack of abnormalities in electromyographic examination and non-specific type 2 fibre atrophy [7, 8]. Low serum CK activity has been found to be associated with muscle weakness, suggesting that alterations in creatine metabolism may be involved [9]. Similar to patients with RA, patients with gyrate atrophy also have type 2 muscle fibre atrophy [10]. In this group of patients, this change in muscle fibre composition is associated with a decrease in the skeletal muscle creatine content which can be corrected by the administration of creatine.

In healthy persons and patients with chronic heart failure, oral administration of high doses of creatine increased the skeletal muscle creatine and phosphocreatine content in most but not all subjects [11–16]. This increase was generally associated with an increase in short-term exercise capacity [13, 15–18], but had no beneficial effect on aerobic exercise capacity [19, 20].

On the basis of these studies, we hypothesized that the administration of creatine may improve the skeletal

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muscle function of patients with RA. We therefore investigated the effects of long-term oral administration of creatine on physical performance and skeletal muscle creatine metabolism of patients with RA.

## Materials and methods

### *Design*

The study was a 3-week open study of creatine supplementation in 12 RA patients fulfilling the American College of Rheumatology (ACR) criteria for RA [21]. It was reviewed and accepted by the Ethics Committee of the Medical Faculty of the University of Zurich.

### *Intervention*

A 3-week supplementation with creatine monohydrate chewing tablets (Wander Pharma, Bern, Switzerland) was given. We administered 20 g/day (four times 5 g) for the first 5 days (loading phase) and 2 g/day (four times 0.5 g) for the remaining 16 days (maintenance phase). This dosage was based on creatine supplementation in clinical [13] and experimental studies [11, 12, 14], in which no side-effects associated with this intervention were reported. According to the protocol, patients were asked not to change their habits and physical activity during the study.

### *Data collection*

All participants were examined on entry and at the end of the study. These investigations included the collection of a blood sample and 24-h urine, a clinical examination, a muscle biopsy (quadriceps) and muscle strength measurements (elbow and knee). In addition, the participants had to complete self-administered questionnaires.

### *Measures*

While isokinetic measurements have been used in studies by Greenhaff *et al.* [17], this type of exercise caused pain to patients with RA in pre-testing. We thus used isometric muscle strength measurements in the form of a muscle strength index (MSI) which has been validated in patients with RA. The MSI includes measurements of knee and elbow extension and flexion. To reduce the burden of measurements we restricted the measurements to the left side of the body (the resulting index is of virtually identical reliability as compared with the test assessing both sides) [5].

To examine physical functional disability we used the Health Assessment Questionnaire (HAQ) [22, 23], one of the most frequently used instruments for measuring functional disability and daily activities in patients with RA. The HAQ measures the capabilities in dressing, arising, walking, hygiene, reaching, gripping, and other activities. The questionnaire is self-administered and takes less than 5 min to complete.

To control for disease activity we used the disease activity score (DAS) which is calculated based on the number of swollen and tender joint counts and the erythrocyte sedimentation rate (ESR) [24]. For the DAS, only 28 and not 68 joints are examined, reducing the burden for the patients without being less accurate [25].

Creatine in serum, urine and skeletal muscle was determined spectrophotometrically according to Bernt *et al.* [26]. Creatine phosphate in skeletal muscle was determined spectrophotometrically according to Lamprecht *et al.* [27]. The coefficient of variation of the technique that was used to measure the muscle creatine and muscle creatine phosphate levels is below 5%. The muscle creatine content is expressed per g tissue wet weight. Laboratory assessment also included the ESR and serum CK activity which were determined by routine methods of clinical chemistry.

### *Analyses and sample size*

The differences between the values before and after treatment were tested by a one-sample *t*-test. The level of significance was set to 0.05. The sample size calculation was based on a one-sided paired *t*-test (pre- and post-medication strength constitute the matched pairs). We calculated that 11 pairs of before and after measurements would be needed to detect an improvement of at least 20% (the assumed minimal difference of clinical importance) with a power of 90% given that such a difference actually exists.

The primary outcome variable tested was the MSI. To examine whether the expected increase in isometric muscle strength would translate into statistically significant and clinically meaningful gains in physical functional ability, we also examined for changes in the HAQ score. Unless stated otherwise, data are presented as mean $\pm$ S.E.

## Results

### *Patients*

We obtained full clinical and questionnaire data from all patients. However, skeletal muscle biopsy was possible in 12 patients at the start of the study but in only nine patients at the end (three patients refused a second biopsy). The mean age of the study population was 54 yr (S.E. = 13), with a range of 28–70 yr. Seventy-five per cent of patients were female. The mean weight was 68 kg (S.E. = 4) and the mean height was 166 cm (S.E. = 3). The medium duration of disease was 9 yr (range 1–26 yr). The rheumatoid factor was positive in 11 of 12 patients.

### *Side-effects and compliance*

During the study period, patients reported no adverse events associated with the ingestion of creatine. All patients maintained creatine supplementation during the whole study period, as assessed by tablet counting and determination of creatine concentrations in serum and urine (see below).

### *Muscle strength and physical functional ability*

Muscle strength as measured by the MSI showed an increase in eight of 12 patients and reached statistical

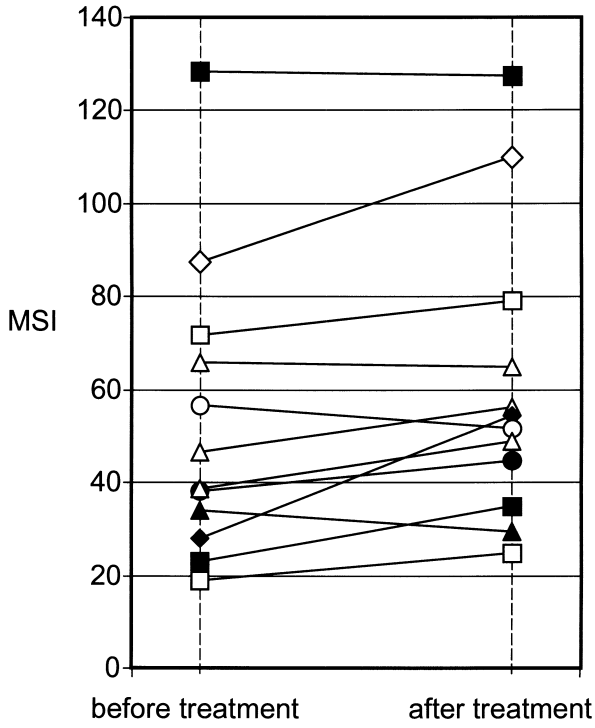


FIG. 1. MSI before and after treatment with creatine. The MSI increased in eight 12 patients, reaching statistical significance ($P = 0.02$).

significance (Table 1 and Fig. 1). Concerning individual joints, muscle strength increased for the index (mean difference = 7.4 percentage units, S.E. = 2.85, $P < 0.02$) and for the flexion of elbow and knee, but was not significant for the extension of elbow and knee ($P = 0.08$). The MSI was associated with physical functional ability as measured with the HAQ both at baseline ($r = -0.71$, $P = 0.01$) and after treatment with creatine ($r = -0.62$, $P = 0.03$). However, physical functional disability (HOQ) did not change significantly with the administration of creatine, whereas disease activity as measured with the DAS showed a significant decrease.

*Creatine metabolism*

As shown in Table 1 and Fig. 2, the skeletal muscle creatine content increased in eight of the nine patients studied with creatine administration ($P = 0.04$). In contrast, the skeletal muscle content of creatine phosphate as well as the total creatine content did not change significantly. The serum creatine concentration and the urinary excretion of creatine increased by a factor of 4 and 30, respectively, with creatine supplementation, suggesting that the patients were compliant. Urinary excretion of creatine at the end of the study was 2 g/day, accounting for 100% of the dose ingested. The serum activity of CK did not change with creatine administration.

*Association between creatine metabolism and muscle strength*

Cross-sectionally, the skeletal muscle creatine content was associated with the MSI at baseline ($r = 0.55$, $P = 0.06$), but not after treatment with creatine ($r = 0.03$). Instead, neither the phosphocreatine nor the total creatine content were associated with the MSI at both time points. Longitudinally, the changes in the MSI following creatine administration were not associated with any of the creatine parameters. Interestingly, the total creatine content increased in three of the four patients with the lowest starting value, and all of these patients showed a concomitant increase in muscle strength.

## Discussion

Our study illustrates that patients with RA can be treated safely with high doses of creatine. Regarding all patients as one group, this treatment is associated with an increase in muscle strength but not in the skeletal muscle creatine content.

The skeletal muscle creatine content in the patients studied was 23 μmol/g wet weight, which corresponds to approximately 115 μmol/g dry weight, assuming a water content of 80% [28]. This value agrees well with the 110–140 μmol/g dry weight reported in studies with

TABLE 1. Clinical and biomedical characterization of the patients studied ($n = 12$). Muscle biopsies could only be obtained from nine patients at follow-up. Data are given as mean (S.E.)

| Measure | Baseline | Follow-up | Change | *P*-value |
|---|---|---|---|---|
| Clinical assessment | | | | |
| MSI | 53.2 (9.1) | 60.6 (9.0) | 7.4 (2.9) | 0.02 |
| HAQ | 1.20 (0.16) | 1.24 (0.17) | 0.06 (0.06) | 0.38 |
| DAS | 4.35 (0.36) | 3.68 (0.32) | −0.67 (0.24) | 0.02 |
| Skeletal muscle | | | | |
| Creatine (μmol/g) | 6.9 (0.7) | 7.4 (1.0) | 1.4 (0.6) | 0.04 |
| Creatine phosphate (μmol/g) | 16.2 (0.9) | 12.3 (1.5) | −3.0 (2.2) | 0.21 |
| Total creatine (μmol/g) | 23.0 (1.3) | 19.7 (2.19) | −1.60 (2.55) | 0.54 |
| Serum | | | | |
| Creatine (μmol/l) | 36.5 (5.9) | 153 (23) | 116 (22) | <0.01 |
| CK (U/l) | 66 (6) | 73 (18) | 7 (16) | 0.29 |
| Urine | | | | |
| Creatine (μmol/24 h) | 450 (200) | 13 900 (1300) | 13 450 (1240) | <0.01 |

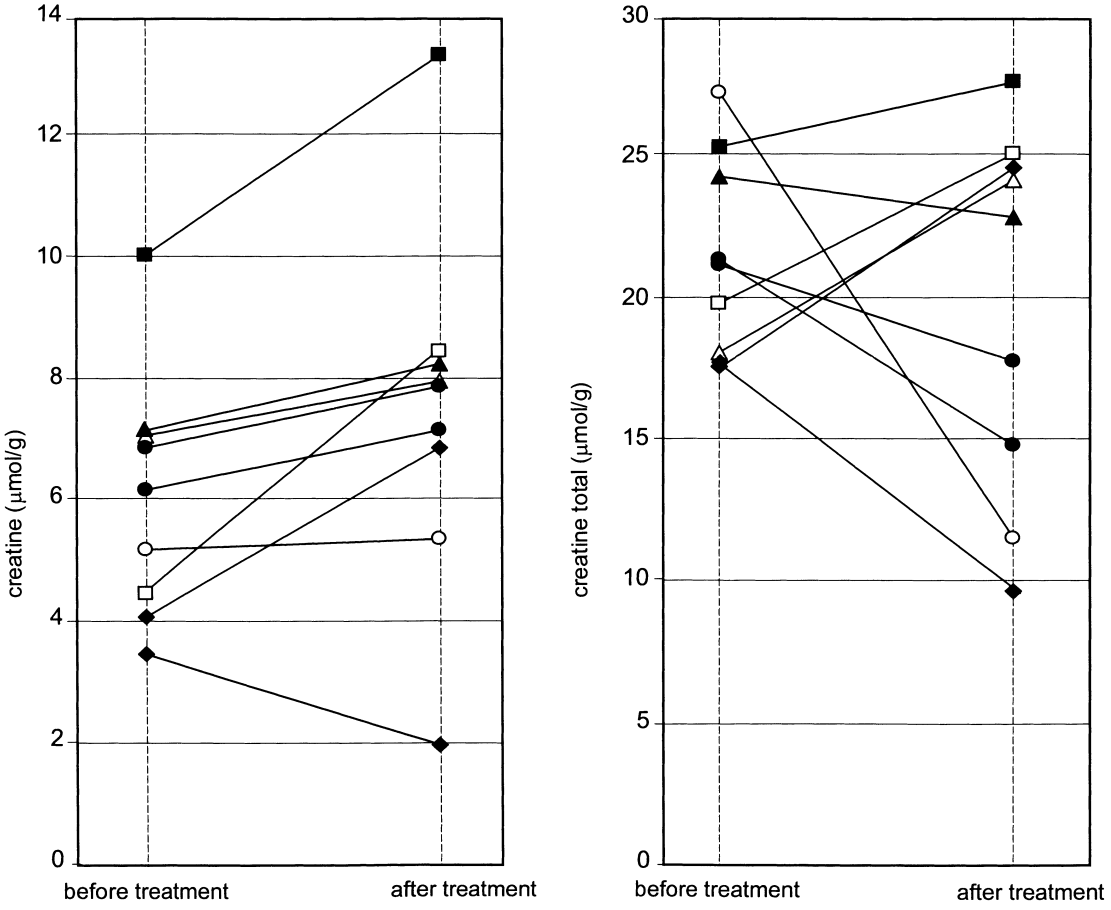


FIG. 2. Creatine content in skeletal muscle before and after treatment with creatine. The creatine content increased in eight of nine patients with treatment (left), whereas the total creatine content (creatine and phosphocreatine) showed no significant change (right).

normal subjects [11–14], suggesting that the skeletal muscle creatine metabolism is not disturbed profoundly in patients with RA. Treatment with creatine led to an increase in the skeletal muscle creatine content in eight of the nine patients, whereas creatine phosphate and the total creatine content did not change significantly. In normal subjects, similar treatments were associated with a 10–20% increase in the total skeletal muscle creatine content in most [11, 13–15] but not all subjects studied [12]. Since poor compliance and technical problems in the quantification of creatine are unlikely to be the reasons for our findings, the exact causes for the lack of increase in the skeletal muscle creatine content in patients with RA remain unclear. As indicated by the urinary excretion of creatine, which equalled the dose administered, reduced absorption of creatine can be excluded. The most probable reasons for our findings include, therefore, alterations in the kinetics of creatine in patients with RA, for instance altered distribution (e.g. reduced transport into skeletal muscle), increased metabolism and/or increased excretion. Since our study was not designed to answer these questions, further studies are necessary to investigate in more detail creatine metabolism in patients with RA.

Creatine supplementation has been shown to be associated with increased muscle strength during short-term exercise in normal subjects [15–18] and in patients with chronic heart disease [13]. On the other hand, no effect of creatine supplementation could be demonstrated in normal subjects performing long-term exercise [19, 20]. These findings are in agreement with the physiological role of the creatine/creatine phosphate system, which provides energy for less than a minute in a maximally working skeletal muscle [29]. The MSI used in the current studies is calculated from the maximal force achieved by different muscle groups during isometric contraction over a short time. This type of muscle contraction corresponds to short-term exercise and could therefore potentially be affected by the skeletal muscle creatine content. Indeed, administration of creatine was associated with an increase in the MSI in eight of 12 patients, reaching statistical significance. This increase cannot be explained by changes in the skeletal muscle creatine content, however, since there was no association between these two variables and the skeletal muscle total creatine content did not increase. On the other hand, there was a significant association between the skeletal muscle total creatine content and muscle

force at baseline, suggesting that an increase in the skeletal muscle creatine content could also potentially result in an increased muscle strength in patients with RA.

Analysis of individual patients reveals that three of the four patients with the lowest starting creatine levels showed an increase in their skeletal muscle creatine content with a concomitant increase in the MSI. A subgroup of RA patients may therefore exist which potentially profits from the administration of creatine. Further studies have to be conducted to confirm this hypothesis and to define this group of patients in more detail.

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