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Creatine supplementation improves muscle strength in patients with congestive heart failure

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Background: Both, cardiac and skeletal muscle creatine levels are depressed in patients with congestive heart failure (CHF). Oral supplementation of creatine (Cr) could increase physical performance in healthy volunteers. We therefore hypothesized that oral creatine supplementation improves skeletal muscle strength, quality of live and symptom-limited performance in patients with CHF.
Methods: In a double-blind, placebo-controlled and crossover-designed study, 20 patients suffering from congestive heart failure more than 6 months and a peak oxygen uptake (peak VO_2) below 20 ml/min/kg received 4×5 g Cr daily vs. placebo for 6 weeks and were crossed over for the following 6 weeks. Peak VO_2, VO_2 at the anaerobic threshold (VO_2AT), ejection fraction (EF), distance in 6-minute-walk-test (6 min W), and muscle strength (Modified Sphygmomanometer (MS)) were determined at baseline, after 6, and after 12 weeks. Dyspnoea after 6-minute-walk-test was measured using the Borg Scale. Quality of live was assessed with the Minnesota Living with Heart Failure Questionnaire (MLHFQ).
Results: 13 of 20 Patients finished the study. After 6 weeks of creatine supplementation there was a significant increase in body weight and muscle strength compared to baseline and placebo ($p < 0.05$). However, there was no significant change in peak VO_2, VO_2AT, walking distance, quality of life assessment and EF.
Conclusion: Short-term creatine supplementation in addition to standard medication in patients with CHF leads to an increase in body weight and an improvement of muscle strength. This effect is restricted to the time of supplementation.

1. Introduction

Creatine (Cr) as a naturally occurring compound plays an important role in the energy metabolism of the skeletal and heart muscle. In the phosporylated isoform (PCr) it acts as a temporal buffer to maintain ATP concentration via rephosphorylation of ADP during intense muscular work. The endogenous synthesis of Cr takes place in liver, kidney and pancreas, however oral intake will contribute to the whole body creatine pool. In a number of studies it has been shown that Cr supplementation substantially elevates muscle total Cr content by 20 to 50%. About 20% of this accounts for PCr. Although Cr loading improves the ability to maintain power output during high intensive muscle work, especially repeated skeleton muscle work (Birch et al. 1994; McNaughton et al. 1998), the effect of Cr supplementation on endurance capacity is unclear (Maganaris and Maughan 1998; Engelhardt et al. 1998).
Patients with congestive heart failure are frequently limited by dyspnoea and exertional fatigue. The symptoms are mainly related to low cardiac output, decreased muscle perfusion and impaired muscle cell metabolism (Toussaint et al. 1998; Mancini et al. 1992). Furthermore in patients with long-term heart failure a fibre atrophy and a change in fibre composition towards an increase of type II fibres occur in skeletal muscle in concert with a decrease in oxidative enzyme capacity (Sullivan et al. 1991). Skeletal muscle biopsies of patients with congestive heart failure have demonstrated a reduction of total creatine content. In addition magnetic resonance imaging could show post-exercise delay in the resynthesis of PCr (Mancini et al. 1988). Therefore, reduced availability of creatine may also contribute to the metabolic abnormalities observed in the myocardium of patients with congestive heart failure (Conway et al. 1991). Cr supplementation is able to increase skeletal as well as cardiac muscle high-energy phosphates (Gordon et al. 1995; Brzezinska et al. 1998) and may improve clinical status and symptoms in these patients.
The following study was undertaken to determine whether supplementation of creatine in patients with congestive heart failure improves physical performance, skeletal muscle strength, and quality of life.

2. Investigations and results

2.1. Study population

Twenty patients were included in a double-blinded, placebo-controlled and crossover-designed study. Inclusion criteria were history of congestive heart failure of more than

6 months, NYHA II and III and a maximal oxygen uptake of less than 20 ml/min/kg body weight. The medication had to be stable for at least 3 months prior to the study. The patients' history had to be free from diseases limiting physical performance other than heart failure, e.g. peripheral artery disease. Patients were excluded if cardiac drugs had to be changed during the study period. The institutional ethics committee approved the study protocol. All patients gave written informed consent. Patients were supplemented either with 5 g creatine or placebo four times daily. After 6 weeks patients were crossed over to the alternative group. At baseline, after 6, and after 12 weeks, the following tests were undertaken:

2.2. Examinations

2.2.1. Cardiopulmonary exercise tests

A symptom limited cardiopulmonary exercise testing (CPX) was performed. Treadmill test (ER 900; Jaeger, Hoechberg, Germany) was started at 25 or 50 W with stepwise increment of 25 to 50 W every 3 min. The expiratory gas was collected and conveyed to a spirometer as well as to an oxygen and carbon dioxide detector. Oxygen uptake (VO_2), carbon dioxide output (VCO_2), instantaneous expiratory gas concentration throughout the respiratory cycle, and minute ventilation (V_E) were measured continuously on a breath-by-breath basis. Peak oxygen uptake (Peak VO_2) was defined as the peak VO_2 that was measured during the treadmill test. VO_2 at the anaerobic threshold (VO_2AT) was detected by the V-slope-method.

2.2.2. Six minute walk test

The test was carried out in a standardized manner and at the same time of the day with a definitive interval to the patients last meal (Bittner 1997). After patients had completed the six-minute walk test they were asked to rate the level of dyspnoea by the Borg scale. This scale rates the level of dyspnoea on a scale of 0 (nothing at all) to 10 (very very heavy) (Wilson et al. 1995).

2.2.3. Minnesota living with heart failure questionnaire

The 'Minnesota living with heart failure questionnaire' (MLHFQ) was described elsewhere (Guyatt 1993). Patients were isolated from their spouses and other individuals might affect the results. The timing of the questionnaire was consistent for each patient throughout the study.

2.2.4. Elbow flexor muscle strength

The elbow flexor muscle strength was obtained with a modified sphygmomanometer (MS). The sphygmomanometer incorporated a 300 mm Hg column and a bladder portion of the cuff, which was folded into for equal parts and the rest of the cuff rolled loosely around. The enrolled cuff was wrapped with several layers of adhesive tape. Before testing the cuff was inflated to a baseline pressure of 30 mm Hg. Patients were tested in a supine position. Their designated upper extremity was positioned with the shoulder abducted about 30°, the elbow flexed 90° and the forearm supinated. The cuff was placed proximal to the styloids on the flexor surface of the forearm. The arm was manually stabilized. Patients had to come to maximum elbow flexion in one to two seconds for around five seconds and the resulting pressure onto the cuff was recorded (Bohannon and Lusardi 1991).

2.2.5. Echocardiography

Echocardiography was performed in standard manner and views.

2.3. Statistical analysis

Statistical analysis was carried out according to the recommendations of Hills and Armitage for crossover trials (Hills and Armitage 1979). Comparison of values of body weight, oxygen uptake, six minute walk test, MLHFQ, elbow flexor muscle strength, Borg scale and echocardiography at baseline, after the placebo period an after the creatine period was conducted by using analysis of variance (ANOVA) for repeated measures followed by Scheffe's procedure for post hoc comparisons of means. A value of $p < 0.05$ was accepted as statistically significant. Results are expressed as mean $\pm$ SD.

2.4. Results

Twenty patients (5 female and 15 male) with congestive heart failure were included into the study. The patients were 59.5 ± 2.6 years old. Twelve patients were in NYHA class II and 8 in class III. The left ventricular ejection fraction was $27.5 \pm 10.2\%$. The aetiology of congestive heart failure was idiopathic dilated cardiomyopathy in 15 patients and ischemic heart disease in 5 patients. All patients received tailored medical therapy including digitalis ($n = 14$), beta-blockers ($n = 12$), angiotensin-converting enzyme inhibitors ($n = 19$), diuretics ($n = 19$), calcium channel blockers ($n = 2$) and aldosterone antagonists ($n = 4$). (Table 1).

Seven patients stopped study medication prematurely (5 male, 2 female). 3 of 7 patients had Cr when stopping medication and 4 of 7 received placebo and stopped medication. Reasons were a cold in 1 patient, a death in 1 patient, and a newly diagnosed breast cancer in 1 patient. 1 patient decompensated acutely and 3 patients stopped without giving any reasons. 1 patient suffered from slight gastric pain lasting around 1 h after creatine ingestion throughout the period of supplementation. Additional side effects of creatine supplementation could not been observed. The baseline characteristics and main results of the 13 patients who finished the study are shown in Tables 1 and 2.

Table 1: Patients' characteristics

Sex (Female/Male)	3/10
Age (years)	58.2 ± 11.3
Weight (kg)	83.6 ± 10.6
NYHA class (I/II/III/IV)	0/7/6/0
EF	28.8 ± 10.3
Aetiology of heart disease	IDC 10, ICHP 3
Medication	
Digitalis	10/13
ACE-Inhibitors	13/13
Beta-blockers	8/13
Diuretics	12/13
Calcium-channel blockers	2/13
Aldosterone-antagonists	3/13

ICMP; ischemic cardiomyopathy; IDC, idiopathic dilated cardiomyopathy; Values are given as mean $\pm$ standard deviation or as frequencies

Table 2: Main results from 13 patients after creatine supplementation and placebo

	Baseline	Placebo	Creatine
Weight (kg)	83.6 ± 10.6	84.3 ± 10.2	85.9 ± 10.3*
EF (%)	28.8 ± 10.3	28.7 ± 7.5	29.8 ± 8.6
LVEDD (mm)	65.9 ± 5.1	65.2 ± 6.5	67.0 ± 5.8
Peak VO_2 (ml/min/kg BW)	13.7 ± 2.5	16.0 ± 4.2	14.8 ± 3.4
VO_2AT (ml/min/kg BW)	11.1 ± 1.9	12.5 ± 2.3	12.2 ± 2.6
6 min WT (m)	581 ± 115	604 ± 103	597 ± 125
Borg Scale	4.9 ± 2.3	4.4 ± 1.7	4.2 ± 1.6
EFMS (mm Hg)	95.8 ± 26.5	88.3 ± 11.9	112.5 ± 14.8*
MLHFQ	34.0 ± 17.1	36.0 ± 15.1	37.2 ± 19.8

EF, ejection fraction; LVEDD, left ventricular diameter in end diastole; AT, anaerobic threshold; 6 min WT: 6 min. walk test; EFMS, elbow flexor muscle strength; BW, body weight; MLHFQ, Minnesota Living with Heart Failure Questionnaire;
*$P < 0.05$ (vs. baseline and placebo)

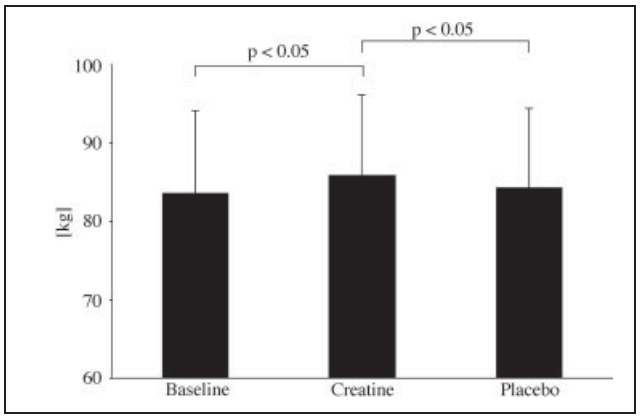

Fig. 1: Effects of supplementation with creatine in a dose of 4×5 g per day over a period of 6 weeks on body weight compared to baseline and placebo in 13 patients finishing the study

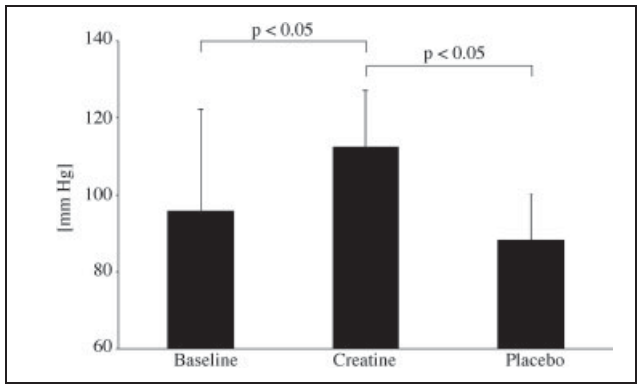

Fig. 2: Effects of supplementation with creatine in a dose of 4×5 g per day over a period of 6 weeks on elbow flexor muscle strength compared to baseline and placebo in 13 patients finishing the study

After 6 weeks of supplementation with creatine there was a significant increase of body weight of 1.6 kg as compared to placebo and 2.3 kg compared to baseline (Fig. 1). Ejection fraction at baseline (28.8 ± 10.3%) did not differ from ejection fraction after 6 weeks of treatment with placebo (28.7 ± 7.5%) and creatine (29.8 ± 8.6%). There was also no difference in the left ventricular enddiastolic diameter after supplementation (Table 2).

All patients terminated cardiopulmonary exercise test because of dyspnoea and muscle fatigue. No patient developed angina during exercise testing. VO_2AT and peak VO_2 at baseline were 11.1 ± 1.9 and 13.7 ± 3.4 ml O_2/min/kg body weight (BW), respectively. There was no significant difference in peak VO_2 between placebo, creatine supplementation and baseline. Regarding anaerobic threshold, again there was no significant difference between creatine supplementation and baseline (Table 2).

The distance covered in a 6-minute walk test at baseline was 581 ± 115 meters. There was neither a significant change with placebo nor with creatine (Table 2).

The measurement of the elbow flexor muscle strength showed a significant increase after creatine supplementation (112.5 ± 14.8 mm Hg) compared to baseline (95.8 ± 26.5 mm Hg) and placebo (88.3 ± 11.9 mm Hg), respectively (Fig. 2).

After finishing the 6-minute walk test patients had to assess their level of dyspnoe using the Borg scale. The perceived dyspnoea did not change significantly between baseline, placebo and creatine supplementation. A significant change in the quality of life self-assessment was not found (Table 2).

3. Discussion

The present study was undertaken to demonstrate a positive effect of creatine supplementation on physical performance and quality of life in patients with congestive heart failure. The study was crossover designed with a 6 weeks period of supplementation with creatine and placebo. This should exclude an overlap of possible creatine effects as complete washout period is around 4 weeks (Febbraio et al. 1995; Hultman et al. 1996), and the creatine-free interval should definitively be long enough to return total muscle creatine to presupplementation levels. The dose of 20 g Cr per day over a 6 weeks period was supramaximal but chosen to exclude possible interindividual variation of Cr uptake, which might influence study results in this small study population. In patients with congestive heart failure a reduction in skeletal muscle creatine content has been demonstrated (Broqvist et al. 1992; Mancini et al. 1988). In our study, VO_2max was depressed corresponding to a moderate to severe congestive heart failure. Therefore a low level of muscle creatine was assumed.

We could demonstrate that creatine supplementation was paralleled by a significant increase in body weight as well as a significant increase in muscle strength. However, after termination of creatine both body weight and muscle strength reverted to baseline. The significant increase in body weight may be a consequence of water retention related to an osmotic load caused by Cr (Maganaris and Maughan 1998; Kraemer and Volek 1999; Volek et al. 1999). Although we did not definitively prove the change in creatine levels via muscle biopsy or NMR-imaging at the end of 6 weeks supplementation, these published data

suggests an increase of creatine levels in muscle cells of our patients

Cardiopulmonary exercise testing is regarded as the standard method to assess the exercise capacity in patients with heart failure. The test allows subjects to reach power output above 90% of maximal oxygen consumption, at least far beyond anaerobic threshold. Under these metabolic conditions, supplementation of creatine is suggested to have beneficial effects on regeneration of ATP and may improve muscle performance and low exercise reserve in patients with heart failure (Gordon et al. 1995). We could not demonstrate a significant increase of oxygen uptake at maximum and at the anaerobic threshold after 6 weeks of creatine supplementation. The distance covered in the 6-minute walk test did also not improve. One reason for unchanged exercise capacity in this type of physical performance may be an increased body weight (Balsom et al. 1993), and another one may be the nature of bicycle ergometry and walk test, where not only muscle cell metabolism, but cardiac output and pulmonary function are critical for exercise limitation.

On the other hand we could demonstrate a significant increase in muscle strength of 15% with creatine supplementation. This improvement is restricted to the phase of creatine supplementation and declines to baseline values during the placebo period. However, this effect has also been noticed in healthy volunteers (Greenhaff et al. 1993; Harris et al. 1992). There is evidence that a change in muscle cell metabolism by means of an increase in protein synthesis (Chanutin 1926; Benedict and Osterberg 1923) is the bottom line of an improvement of muscle strength after creatine supplementation. Furthermore, Sipila et al. (1981) demonstrated a reversal of type II muscle fibre atrophy in patients suffering from gyrate atrophy, and Brannon et al. (1997) have shown a muscle hypertrophy consisting predominantly of type II muscle fibres in a rat model, when creatine supplementation was combined with training. Accordingly, Becque et al. (2000) could demonstrate an increase of arm flexor muscular strength and upper arm muscle area, both of 11% after a 6 weeks period of resistance training and creatine supplementation. Altogether, patients with congestive heart failure respond to creatine supplementation, which is thought to be beneficial. But does an increase in muscle strength subsequently improve quality of life? We could not demonstrate changes in quality of life and physical performance. However, only eight questions of the 'Minnesota living with heart failure questionnaire' focus primarily on physical limitation and none is related to activities that are mainly related to muscle strength. Therefore, the questionnaire may not record changes in quality of life on the basis of short-term use of muscle strength, which nevertheless play a role in daily physical activity.

A change in ejection fraction and left ventricular diameters, although not end points in our study, could not be observed after supplementation with creatine. Uptake and potential effects of creatine in cardiac muscle cells is still questionable. Horn et al. (1998) did not find an increase of creatine content and myocardial energy reserve after creatine feeding in rats. Furthermore, they could not find an improvement in cardiac function after a myocardial infarction in creatine feeded rats (Horn et al. 1999). In contrast, it has been shown by Brzezinska et al. (1998) that in short-term creatine fed rats phosphocreatine and ATP were elevated in myocardium accompanied by an increase in the mitochondrial oxidative potential. Moreover there is evidence that creatine supplementation is sufficient to attenuate metabolic stress in rat myocardium induced by *N*-nitro-L-arginine methyl ester (L-NAME), a specific inhibitor of nitric oxide synthase, by reconstitution of high energy phosphates (Constantin Teodosiu et al. 1995). None of the present studies addressed the question whether supplementation of creatine improves both creatine content and cardiac performance in creatine deficient hearts, although it is known that a low phosphocreatine-to-ATP ratio is a predictor of cardiovascular mortality in patients with heart failure (Neubauer et al. 1997), and uptake of creatine is dependent on creatine preload of muscle cells (Harris et al. 1992). It could be suggested that a potential effect of creatine supplementation is beneficial especially in these patients. At last, a change in ejection fraction could only be expected in a larger patient population since intra- and interobserver-variability is substantial. The low number of patients is a major limitation of our study.

In conclusion, we could demonstrate an increase of muscle strength in patients with heart failure as a consequence of creatine supplementation, whereas no effect could be seen in aerobic and anaerobic exercise capacity as well as in quality of life. Further studies should evaluate the benefit of creatine and focus on patients with a low basal level of muscle creatine at baseline.

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