Creatine supplementation as an exercise performance enhancer for patients with COPD? An idea to run with

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Creatine supplementation may enhance pulmonary rehabilitation in patients with COPD, but larger trials are needed

Multidisciplinary pulmonary rehabilitation now has an established place in the management of chronic disabling respiratory diseases, particularly chronic obstructive pulmonary disease (COPD).[1] Rehabilitation is being taken up widely on the strength of the accumulated evidence. While the effectiveness of rehabilitation is accepted, there is still considerable interest in refining and researching the individual modalities of treatment that make up the multidisciplinary intervention.

Exercise training is a key component of an effective pulmonary rehabilitation programme. In recent years a number of approaches have been taken in an effort to enhance the effectiveness of physical training, particularly for more severely disabled patients who may have reduced muscle bulk and whose baseline exercise capacity is particularly low. Broadly, strategies have either concentrated on acute interventions that enable subjects to train at higher intensity or have focused on altering underlying skeletal muscle functioning. An example of the former approach is the inclusion of oxygen supplementation during training in patients with hypoxaemia.[2 3] Acute oxygen supplementation does enhance exercise performance and allows a higher work output for training. However, its use in training programmes has not been found to improve the overall outcomes of rehabilitation. Taking the alternative approach, attempts to restore muscle function have seen a crossover of techniques used for performance enhancement in sport and other areas of medicine. These interventions have included nutritional supplementation,[4] the use of anabolic steroids,[5] and the use of growth hormone.[6] These kinds of intervention do increase muscle bulk but do not tend to produce beneficial gains in terms of whole body exercise and patient based outcomes in patients disabled by COPD and low muscle mass.

The underlying causes of the reduction in muscle mass in patients with COPD are likely to be heterogeneous and complex. They include imbalance in caloric intake and expenditure, disuse, the systemic effects of glucocorticoid steroid treatment, low circulating androgen levels, and systemic inflammation. The high prevalence of low muscle mass in patients with COPD is now recognised, as is the adverse impact of malnutrition in terms of disability, health service usage, and mortality.[7]

THERAPEUTIC USE OF CREATINE SUPPLEMENTATION

Set alongside these developments, there has been a growing interest in recent years in the potential for creatine supplementation to benefit various patient groups. When used as a dietary supplement, creatine monohydrate increases the availability of phosphocreatine in skeletal muscle. Phosphocreatine contributes a store of high energy phosphate bonds available at the onset of exercise. Following dephosphorylation, the creatine then becomes available for subsequent regeneration of phosphocreatine. A further effect of creatine is to increase fat-free mass by mechanisms that are not fully understood but which may have to do with muscle water content. In view of these effects, creatine monohydrate has become widely used to enhance athletic exercise performance, particularly in activities characterised by short bursts of activity rather than sustained effort. As with other interventions, creatine supplementation has also made the jump to application in disease states.

In a recent review of therapeutic creatine supplementation, Terjung *et al*[8] highlighted a number of conditions including neuromuscular diseases where possible benefits to exercise capacity, muscle strength, and muscle mass may be seen. Mathews *et al*[9] reported potential neuroprotective effects related to oxidative stress in an animal model of Huntington's disease.[9] The potential for improved cardiac function and skeletal muscle performance in congestive heart failure with creatine supplementation has also been studied.[10] The direct effect of creatine supplementation on lung function, enzymatic activity, and muscle strength in patients with cystic fibrosis has recently been reported in a pilot study.[11] The authors concluded that, although no change in lung function or enzymatic activity in respiratory epithelial cells was evident, improvements in muscle strength and general wellbeing were seen. A number of studies have addressed the potential benefits of creatine supplementation in the elderly. Although most studies have failed to find significant effects,[12] a more recent study[13] identified significant increases in muscle strength, fat free mass, and total body mass when creatine supplementation was offered in combination with resistance training.

CREATINE SUPPLEMENTATION IN COPD

With this background, it is perhaps surprising that the effect of creatine supplementation on muscle mass and muscle function in patients with COPD has been very little researched. This situation begins to be remedied by a paper in this issue of *Thorax*.

Fuld and colleagues[14] report a randomised controlled trial of creatine monohydrate supplementation as an adjunct to exercise training in patients with moderately severe COPD. Their subjects received a standard 2 week loading regimen followed by a maintenance dose of creatine monohydrate or placebo in a randomised double blind fashion. After the loading phase, subjects participated in an exercise training programme of two sessions per week for 16 weeks. Training sessions included mobility and strength training together with 20 minutes of endurance training on a static bike. The primary outcome variable was 10 metre incremental shuttle walk distance. Secondary outcomes were body composition, muscle strength, and cardiopulmonary responses to incremental exercise testing and disease specific health status. Although this was essentially a negative study with respect to its primary outcome variable, the authors present intriguing secondary outcome data. Firstly, fat-free mass increased on average by 1.1 kg in the creatine supplemented group, significantly more than in the placebo group after the loading phase. At the same time, significant benefits in indices of upper and lower limb muscle functioning were seen in the creatine group compared with the

placebo group. While the findings for isolated muscle work were consistent, no discernible trend or significance for between-group differences was seen in response to whole body exercise, either on the cycle ergometer or corridor walking tests. Thus, once again, apparent benefits at a muscle level were not translated into improvements in the integrated response to whole body exercise. Outcomes following exercise training while continuing creatine supplementation were compared with the pre-creatine baseline. Improvements were seen in terms of fat-free mass and limb muscle functioning following training in both groups, but the gap between the creatine supplemented and placebo groups widened. Again, indices of the response to cycling and walking exercise changed inconsistently. Shuttle walking tests showed significant improvements after training but without appreciable differences between groups. Perhaps the most tantalising finding of the study is the significantly greater improvement seen in the creatine supplemented group in St George's Respiratory Questionnaire (SGRQ) score after training. There are certainly problems in interpreting the results from this questionnaire in groups of patients as small as 11. However, the suggestion that creatine supplementation can lead to improvements in health status while improving individual muscle function independently of any effect on walking capacity is of great interest.

IMPLICATIONS OF STUDY

Everyday life is a series of varying transitions from one level of exercise to another and does not often approximate to the conditions of an incremental or endurance shuttle walk test. The physiological effect of creatine is postulated to be as a result of increased ready availability of high energy phosphate bonds within the muscles. These can be used to sustain work rate increases anaerobically until increased oxygen delivery to the muscle can sustain oxidative metabolism and eventually repay the oxygen deficit. The effect of creatine supplementation might therefore support the bioenergetic response to changes in work output. It might be that improving the ''flexibility'' of response to short step changes in work output is what is driving improvements in health status in this study. While this is an attractive hypothesis, there is a problem with the confident interpretation of the present study. Exercise training was accompanied by a surprising decrement in SGRQ scores in the non-supplemented group, whereas clinically important improvements were seen in the creatine supplemented group. In a group of patients prone to exacerbation and unexpected changes in health, much larger numbers of subjects would be needed to provide results confidently applicable to the generality of COPD patients. Additionally, this study begs the question as to whether similar effects would be seen in the context of multidisciplinary rehabilitation rather than pure exercise training.

Thus, as many questions are raised as are answered in the study reported by Fuld and colleagues. However, there is a prime facie case to answer as to whether creatine supplementation will indeed enhance the outcome of pulmonary rehabilitation in its more usual multidisciplinary format. The challenge now is to undertake a large randomised controlled trial, powered to detect clinically important differences in health status, to test this hypothesis. We will then be able to determine the potential usefulness of creatine supplementation in the context of multidisciplinary pulmonary rehabilitation for patients disabled by COPD.

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REFERENCES

1 **Lacasse Y**, Brosseau L, Milne S, *et al*. Pulmonary rehabilitation for chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews* 2003.
2 **Rooyackers J**, Dekhuijzen P, van Hardwaarden C, *et al*. Training with supplemental oxygen in patients with COPD and hypoxaemia at peak exercise. *Eur Respir J* 1997;**10**:1278–84.
3 **Garrod R**, Paul E, Wedzicha J. Supplemental oxygen during pulmonary rehabilitation in patients with COPD with exercise hypoxaemia. *Thorax* 2000;**55**:539–43.
4 **Steiner M**, Barton R, Singh S, *et al*. Nutritional enhancement of exercise performance in chronic obstructive pulmonary disease: a randomised controlled trial. *Thorax* 2003;**58**:745–51.
5 **Creutzberg E**, Wouters E, Mostert R, *et al*. Role for anabolic steroids in the rehabilitation of patients with COPD? A double-blind, placebo-controlled, randomized trial. *Chest* 2003;**124**:1733–42.
6 **Burdet L**, de Muralt B, Schutz Y, *et al*. Administration of growth hormone to underweight patients with chronic obstructive pulmonary disease. A prospective, randomized, controlled study. *Am J Respir Crit Care Med* 1997;**156**:1800–6.
7 **Landbo C**, Prescott E, Lange P, *et al*. Prognostic value of nutritional status in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999;**160**:1856–61.
8 **Terjung RL**, Clarkson P, ER E, et al. The physiological and health effects of oral creatine supplementation. *Med Sci Sport Exerc* 2000;**32**:706–17.
9 **Mathews RT**, Yang L, Jenkins BG, *et al*. Neuroprotective effects of creatine and cyclocreatine in animal models of Huntington's disease. *J Neurosci* 1998;**18**:156–63.
10 **Gordon A**, Hultman E, Kaijser L, *et al*. Creatine supplementation in chronic heart failure increases skeletal muscle creatine phosphate and muscle performance. *Cardiovasc Res* 1995;**30**:413–8.
11 **Braegger CP**, Schlattner U, Wallimann T, *et al*. Effects of creatine supplementation in cystic fibrosis: results of a pilot study. *J Cystic Fibrosis* 2003;**2**:177–82.
12 **Tarnopolsky MA**. Potential benefits of creatine monohydrate supplementation in the elderly. *Curr Opin Clin Nutr Metabol Care* 2000;**3**:497–502.
13 **Brose A**, GP, Tarnopolsky MA. Creatine supplementation enhances isometric strength and body composition improvements following strength exercise training in older adults. *J Gerontol* 2003;**58**:11–9.
14 **Fuld JP**, Kilduff LP, Neder JA, *et al*. Creatine supplementation during pulmonary rehabilitation in chronic obstructive pulmonary disease. *Thorax* 2005;**60**:531–7.