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# **Creatine Supplementation in Humans**

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## **1. HISTORICAL PERSPECTIVE**

In 1928 a book within a "Monographs on Biochemistry" series was published with the title creatine and Creatinine [1]. The book, which was written by Andrew Hunter a Professor of Biochemistry in the University of Toronto, contained over 800 references. These references include several reports of creatine supplementation experiments where creatine, extracted from fresh meat and/or urine, was administered to both humans and animals. In these early creatine supplementation studies, which included measurements on the creatine content of the urine, it was observed that not all of the ingested creatine was excreted from the body. The fate of this creatine was established by Myres & Fine [2] and Folin & Denis [3] who discovered that the creatine content of skeletal muscle from cats and rabbits increased after the animals had been fed with creatine.

One of the earliest reports of creatine feeding with human subjects was carried out by Chanutin in 1926 [4]. In one part of this study a male subject was administered a total of 270 grams of creatine over a period of 20 days. Chanutin was able to show, by measuring the content of creatine in the urine, that approximately 20% of the creatine administered was retained in the body.

It was not until over half a century later that Harris and co-workers [5] were able to confirm, with direct evidence, that the total creatine (TCr) concentration in the skeletal muscle of humans could be increased with creatine supplementation. Following this experiment, several studies have investigated the influence of creatine supplementation on exercise performance in humans.

## 2. THE TOTAL CREATINE POOL IN HUMANS

The total creatine pool in the human body is the combined amount of creatine in its free (Cr) and phosphorylated (PCr) form. Approximately 95% of this total creatine pool is found

in skeletal muscle where the average concentrations of Cr and PCr are approximately 50 and 75 mmol/kg (dm) respectively [6]. These concentrations are subject to individual variations and influenced by factors such as muscle fibre type composition, age, disease and the content of the diet, but apparently not by training status or gender [cf 7].

In humans, there is a daily turnover of creatine to creatinine of approximately 1.5% of the total creatine pool. Thus, for a 70 kg person with a total creatine pool of 120 g, this represents a turnover of approximately 2 g per day. In normal circumstances about 50% of the daily creatine requirement is attained from the diet, primarily from meat and dairy products, whilst the remaining 50% is produced endogenously from the amino acids glycine, arginine and methionine. On a creatine free diet, as is often the case with vegetarians, daily needs must be met exclusively via endogenous synthesis. The enzymes involved in the *de novo* synthesis of creatine are located in the liver, pancreas and kidneys which means that creatine must be transported into the muscle via the bloodstream.

### 2.1. Influence of creatine supplementation

It has now been established, from direct measurements of freeze dried muscle biopsy samples taken at rest, that the total creatine pool, and thus the total creatine concentration of skeletal muscle can be increased following a period of creatine feeding [5]. In agreement with earlier findings [4], Harris and co-workers [5] were able to confirm that during a period of creatine supplementation the greatest uptake occurs over the initial days of feeding. Furthermore, with daily doses of 20 g or more, no further uptake is evident after 5-7 days of supplementation. One factor which appears to increase creatine uptake into the muscle is exercise. It has been shown that during a period of creatine supplementation the uptake of creatine was greater in an exercised leg compared to a control (non-exercised) leg [5].

In a recent study, Hultman and co-workers [8] administered 20 g of creatine monohydrate per day to a group of male subjects (n=31) over a 6-day period. Two sub-groups were then formed and for the following 30 days one group (group 1) were administered 2 g of creatine per day while no creatine was administered to the other group (group 2). The main finding was that TCr concentrations in *M. Vastus Lateralis* were elevated by approximately 20% above control levels following the high dose period of 6 days and remained elevated in group 1 during the subsequent 30 day "low dosage" administration period but returned to control values in group 2. This latter finding has also been reported by Febbraio and co-workers [9].

The majority of the creatine supplementation studies published in the literature have been conducted on male subjects. In a recent study the uptake of creatine in a group of 16 female subjects has been investigated (unpublished findings). Preliminary findings from this study suggest that creatine uptake in females is of a similar magnitude to that observed with male subjects.

Increases in TCr concentration following creatine feeding are subject to large individual variances. In a study where TCr concentrations were measured from muscle biopsy samples before and after a short term supplementation period, it was concluded that the greatest uptake occurred in those subjects with the lowest resting values in the control trial, whilst smaller uptakes were found in those subjects with relatively high resting values [5]. Of

particular interest in this study was the finding that creatine uptake was greatest in two vegetarian subjects. It has been previously suggested that vegetarians have relatively low resting values of TCr [10]. Inter-subject variance in creatine uptake with creatine feeding may affect the results of experiments where metabolic and/or performance measurements are made [cf 11]. To determine the extent, if any, of creatine uptake with supplementation, direct measurements of muscle TCr concentrations, or the creatine content of the urine, need to be made.

# **3. EXERCISE PERFORMANCE**

In the last few years several authors have investigated the influence of creatine supplementation on exercise performance. In the studies reviewed below, two distinctive types of exercise have been identified; i) supramaximal (>100%  $VO_2max$ ) "high intensity" exercise and, ii) continuous sub-maximal exercise.

#### 3.1. High intensity exercise

The results of laboratory based double-blind creatine supplementation studies with high intensity exercise protocols have been inconsistent. One reason for this may be attributed to differences in the exercise protocols. There is, however, evidence which suggests that performance during repeated short duration bouts of very high intensity exercise may be enhanced following a 5-7 day period of creatine supplementation [12-16]. This was illustrated in a study using an exercise protocol consisting of ten 6 s bouts of high intensity exercise, interspersed with 30 s recovery periods [12]. In this double-blind study, which was performed on a Cardionics cycle ergometer [see 17], 16 subjects were randomly assigned to either a creatine or placebo group. The exercise protocol was performed before and after a 6-day administration period which consisted of either 20 g doses of creatine monohydrate (creatine group) or similar doses of glucose (placebo group), per day. During each 6 s exercise period subjects were instructed to try and maintain a pedalling frequency of 140 rev/min. As can be seen in Figure 1, subjects were better able to maintain the target speed along the 10 trials following creatine supplementation. No significant improvements in performance were found in the placebo group.

In a follow up study using a similar exercise model and the same regime of creatine feeding, the ability to sustain a high power output during a 10 s exercise period, performed 40 s after the completion of five standardised 6 s bouts of high intensity exercise, improved significantly following creatine supplementation [14]. The study was designed so that the same amount of work was performed over the five 6 s exercise bouts on both test occasions. An additional finding in this study was that immediately after the fifth exercise period, the muscle lactate concentration was approximately 70% lower after compared to before supplementation. The reason for this finding is not clear. One possible explanation could be that there was a down regulation of glycogenolysis during exercise due to a decrease in the production of free AMP, which is a known activator of *phosphorylase a*.



Figures 1a and 1b. Performance data (mean pedalling frequencies) for the ten 6 s exercise periods of high intensity cycling for the creatine group (n=8 males), before (figure 1a) and after (figure 1b) a 6-day administration period (20g/day) [12].

In a recent study with female subjects, performance during twelve 6 s bouts of all-out exercise on a cycle ergometer [cf 17] was compared before and after a 6-day supplementation period which consisted of either 20 g of creatine (creatine group n=8) or 20 g of glucose (placebo group n=8) per day [18]. The twelve 6 s sprints were divided into 3 sets of 4 sprints, with 30 s rest between each of the four sprints and 2 min of rest between each set. The resistance applied to the flywheel was 7.5% of body weight. The performance data from this study are presented in Figure 2. No significant increase in performance could be attributed to the creatine supplementation. However, of interest in this study was the relatively small decrease in performance observed over the twelve trials.



Figures 2a and 2b. Performance data (mean pedalling frequencies) for the twelve 6 s cycle sprints before (///) and after ( $\blacksquare$ ) the 6 day creatine (Fig 2a; n=8 females) and placebo (Fig 2b: n=8 females) administration period.

With longer repeated bouts of high intensity exercise findings have been inconsistent. In a study using four standardised 60 s bouts of supramaximal exercise on a cycle ergometer, interspersed with 60 s recovery periods, followed by a fifth bout to fatigue, Febbraio and coworkers [9] did not find any difference in performance between a creatine group who were administered 20 g of creatine monohydrate per day for 5 days and a placebo group.

In double-blind studies where a single bout of high intensity exercise has been used, no improvement in performance has been found following creatine supplementation [14,19,20].

It has been suggested that the improvements in performance observed during high intensity intermittent exercise with very short duration exercise periods following creatine supplementation, may be explained, at least in part, by an increased availability of PCr in the working muscle before the start of each exercise period. This may be due to several factors such as a higher pre-exercise (resting) PCr concentration, a smaller decrease in muscle pH following each exercise period and a higher rate of PCr resynthesis during intervening recovery periods. However, more controlled laboratory research is needed in this area.

### 3.2. Endurance exercise

Creatine supplementation does not appear to improve performance or influence substrate utilisation during continuous sub-maximal exercise. In one double-blind study the effect of creatine supplementation (20 g per day for 6 days) on continuous endurance running (a 6 km cross-country course with an undulating terrain) was investigated [21]. No improvement in the time taken to complete the course was found following creatine supplementation. In this study there was a significant deterioration in performance following creatine supplementation, with no corresponding changes in the placebo group. It was suggested that this impairment in performance may have been partly due to the increase in body weight associated with creatine feeding (see Section 4.1). In the same study, time to exhaustion and peak oxygen uptake were measured during a supramaximal treadmill run (mean exercise time approximately 4 min). No differences were found in either group following the supplementation period.



Figure 3. Peak oxygen uptakes (ml/kg/min) measured during the supramaximal run to exhaustion before vs after 6-day administration period with either creatine ( $\bigcirc$  n=7 males) or a glucose placebo (O n=7 males). (after Balsom *et al.* [21])

In a study by Stroud and co-workers [22] eight male subjects performed a continuous incremental exercise test, which consisted of 6 min workloads at varying sub-maximal intensities, before and after 5 days of creatine supplementation. No significant differences were found (before vs after) in respiratory gas exchange and blood lactate measurements, which were recorded during the last 30 s of each workload. It was concluded that creatine supplementation did not influence substrate utilisation during continuous sub-maximal exercise.

## 4. SIDE-EFFECTS

The only documented side-effect which has been consistently associated with creatine supplementation, where daily doses have not exceeded 20 g and the administration period has not exceeded 7 days, is an increase in body mass. In two studies by Balsom *et al.* [12,21] a mean increase in body weight of around 1 kg was reported (n=17) for subjects administered 20 g of creatine monohydrate per day, for 6 days. There is, however, no documented evidence to indicate whether there are any side-effects caused by supplementation if higher doses are administered for longer periods of time.

Isolated incidents of diarrhoea have been reported from people ingesting creatine. The most likely explanation for this is that the creatine had not been completely dissolved in a liquid before ingestion. Recently, there have been anecdotal reports from several groups of elite sprint athletes, who have ingested creatine on a regular basis, of a higher incidence of muscle cramps.

## 4.1. Increase in body mass

The findings from two recent studies suggest that the increase in body weight found as a result of creatine supplementation may be due to an increase in fluid retention. In one of these studies (unpublished data) a female subject consumed exactly the same quantity of food and fluids over two separate 4-day periods. The only difference between the two 4-day periods was that during the first control period she consumed 80 g of glucose (20 g per day) and during the second experimental period she consumed 80 g of glucose and 80 g of creatine monohydrate (20 g per day). The subject did not exercise during either of the two 4-day periods. During both 4-day periods urine was collected and body weight was measured each morning. The results from the urine and body weight measurements are shown in Figure 4. It can be seen that the increase in body weight during the period of creatine supplementation was accompanied by a marked decrease in urine production. This is in agreement with the findings of Hultman and co-workers [8].



Figure 4. Body mass (left) and volume of urine excreted (right) for one female subject during two four day periods with standardised food and fluid intake ( $\Box = 4$  day control period and  $\bigoplus = 4$  days with creatine [20g/day]

# 5. USE AS AN ERGOGENIC AID IN SPORT

In recent years there has been a rapid growth in the use of creatine supplementation as a potential ergogenic aid in sport. It is still unclear in which sporting disciplines, if any, performance may be enhanced. In the sprint disciplines of running, swimming and cycling there are many anecdotal reports of improvements in performance following creatine supplementation. These reports, however, are not supported by evidence from controlled double-blind studies. In swimming, Mujika *et al.* [23] did not observe any increases in either 25, 50 or 100 m performance before vs after a 5-day period of creatine supplementation (20 g per day).

In sporting disciplines with continuous sub-maximal exercise of a longer duration creatine feeding may actually impair performance.

In many team ball games and racquet sports e.g., football, basketball, ice hockey and tennis, the exercise pattern is characterised by high intensity intermittent exercise, in which, periods of high intensity exercise are interspersed with periods of lower intensity exercise or standing still. In these sports, although it not possible to evaluate performance objectively during match-like situations, it has been suggested that creatine supplementation could enhance performance. However, any isolated short term benefits on performance in these sports, where game time often exceeds one hour, may be counteracted by an increase in body weight.

In combat sports such as boxing, judo and Olympic wrestling, where weight restrictions are imposed, increases in body weight of over 1 kg may be unacceptable. Furthermore, in a

recent study, Smith and co-workers [24] did not find any improvements in simulated boxing performance as a result of creatine supplementation.

In the context of sport it would be of interest to study the effects of long term creatine supplementation (e.g. during a competitive season) as opposed to acute supplementation on exercise performance. Further work is needed in this area to clarify whether creatine may be classified as an ergogenic aid in sport.

# 6. DOPING

It is beyond the scope of this article to discuss whether creatine should or should not appear on the IOC doping list. It should be pointed out that there is currently no blood or urine test able to detect the long-term ingestion of orally administered creatine.

## 7. ACKNOWLEDGEMENTS

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#### **Discussion:** Creatine Supplementation in Humans

## P.M. Clarkson:

Most of the studies on creatine have been done to assess the effects on performance. However, most of the marketing is done for its claim to increase muscle mass. You discussed the increase in body weight was possibly due to increased fluid accumulation. Is it likely? Anecdotally, athletes believe that creatine does increase muscle mass to some extent. Do you believe that your data on fluid retention can explain the entire increase in body weight that is seen with creatine?

## P.D. Balsom:

In some subjects we have seen increases in body weight of around 2 kg following 6 days of supplementation with 20 gram doses per day. It would seem reasonable to assume, even without making any measurements, that at least a part of this is due to fluid retention. The data which shows that urine production is reduced during creatine supplementation does in fact suggest that, if not all, then at least a major part of the increase in body weight is due to fluid retention.

#### F. Brouns:

If it is pure water, you could look at whole body water measurements by using stable isotopes. That is one possibility. Another possibility is looking at different fluid compartments.

#### T.D. Fahey:

On an Internet discussion group in sports medicine, several team physicians in the United States have commented on an increased incidence of muscle cramps in football players. They think it might be due to creatine supplementation. Could you comment on that?

## P.D. Balsom:

We have a group of Swedish sprinters who have complained of the same thing and they have actually now stopped taking creatine because they did associate an increase in muscle cramps with creatine supplementation.

### F. Brouns:

There are data on the linear relationship between creatine increase in muscle and muscle glycogen increase. If you look to sprinters, mostly they complain of the lower leg. May be a supra-normal increase in muscle volume due to glycogen and water uptake, is causing these complains. The muscle fascia is too rigid to adapt on a short-term and this may lead to an increased intra-muscular pressure reducing capillary blood flow. This is comparable to the loge syndrome after rapid muscle hypertrophy and may be a cause of the muscle campring.

### D.P.M. MacLaren:

We have carried out a preliminary investigation using a training study, where we had some elite club rugby league players who in a six-week period with creatine loading vs placebo condition showed significant improvements in strength and various power measurements.

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### J.B. Leiper:

We have recently carried out a double blinded cross-over study in males who were weight training. There was an increase in maximum voluntary contraction in subjects only when they were creatine supplemented, and we did observe a reduction in urine output over virtually the whole time they were on the creatine supplementation.

# G. Atkinson:

In the case study on the female athlete, where she was given placebo for a period of time and creatine for a period of time, was the stage of the menstrual cycle noted? This can affect fluid retention.

## P.D. Balsom:

Yes, we did. We took it 5 days into a new cycle. We were advised that this would be a good time.

#### G. Atkinson:

If there was a change in body mass with the creatine and you were measuring performance, could you express the performance measures relative to the body mass, to see if any changes were there independent of changes in body mass?

### P.D Balsom:

I do not think it would be appropriate in a cycling study because we are sitting during the cycling. Obviously, that would be a more appropriate consideration in any running studies.

## A.D. Martin:

I think we have a real problem in body composition trying to measure muscle mass. Unfortunately, we are wonderful at trying to measure fat, but in the world of performance, muscle is far more important and yet, it is much more difficult to measure. The classic method of urinary creatinine excretion is obviously useless when you are trying to look at the effects of creatine.

## F. Brouns:

Maybe MRI imaging is a possibility. People are working on that. Curiously, body mass does not always increase although there may be significant increase in total creatine in muscle.

#### P.D. Balsom:

I have a question to Dr. Cowan. What is your view on creatine?

### **D.A. Cowan:**

This is one of the things we have not covered in any depth when dealing with what should be controlled and what should not be. Although we have spoken about the side: "Could it enhance performance?" which certainly is one of the rationales for including the substance as a prohibited substance. The other side: "Is it harmful to health?" The International Olympic Committee certainly say that they want to look at the harmful side as well.