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Journal of Sports Sciences
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713721847

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Online Publication Date: 01 February 2002
To cite this Article: Harris, Roger C., Nevill, Mary, Harris, D. Beorn, Fallowfield, Joanne L., Bogdanis, Gregory C. and Wise, John A. (2002) 'Absorption of creatine supplied as a drink, in meat or in solid form', Journal of Sports Sciences, 20:2, 147 - 151
To link to this article: DOI: 10.1080/026404102317200855
URL: http://dx.doi.org/10.1080/026404102317200855

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Journal of Sports Sciences, 2002, **20**, 147–151

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Absorption of creatine supplied as a drink, in meat or in solid form

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Accepted 3 October 2001

We examined the plasma concentration curve obtained over 6 h after the ingestion of 2 g of creatine (Cr) (equivalent to 2.3 g $Cr \cdot H_2O$) contained in meat or in solution in five non-users of creatine supplements. Peak plasma creatine concentration was lower after the ingestion of meat but was maintained close to this for a longer period. Measurements of the area under the plasma concentration curve indicated approximate bioequivalence of creatine contained in meat with the same dose supplied in a solution. In a separate study, we examined the plasma concentration–time curve after ingestion of solid $Cr \cdot H_2O$. Creatine ingested as a lozenge (crushed in the mouth and swallowed) or as a crystalline suspension in ice cold water resulted in a 20% lower peak concentration and 30–35% smaller area under the plasma creatine concentration curve than the same dose administered in solution. Despite a possibly lower bioavailability, 2.3 g $Cr \cdot H_2O$ supplied in either solid form was nonetheless sufficient to raise the plasma concentration five- to six-fold in individuals with a mean body mass of 75.6 kg. We conclude that creatine administered as meat or in solid form is readily absorbed but may result in slightly lower peak concentrations than when the same dose is ingested as a solution.

Keywords: absorption, creatine, diet, meat, pharmacokinetics.

Introduction

Creatine (Cr) supplied in solution is readily absorbed from the gut (Crim *et al.*, 1976; Harris *et al.*, 1992), while repeated oral administration for several days results in an increase in its concentration in muscle in most people (Harris *et al.*, 1992). Elevation of the muscle creatine content has been shown to increase an individual's capacity for sustained or intermittent intense exercise (Greenhaff *et al.*, 1993; Harris *et al.*, 1993), although it appears to have less of an effect on the performance of endurance exercise performed at submaximal work loads (Balsom *et al.*, 1993; Stroud *et al.*, 1994). Today, supplements containing $Cr \cdot H_2O$ are readily available and widely used by athletes and non-athletes in the hope of improving physical performance.

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The question of whether the use of creatine in sport is ethical or not has frequently been raised in the media. Creatine occurs naturally in the human diet and, in some societies, in amounts close to those recommended to be taken as a supplement. Red meat and fish contain 4–10 g creatine per kilogram (Balsom *et al.*, 1994; Harris *et al.*, 1997), while supplementation programmes frequently begin with multiple doses per day of 4.4 g creatine (5.0 g of $Cr \cdot H_2O$). However, we are not aware that the absorption of creatine from the ingestion of meat has ever been compared to its absorption when supplied as a drink, the most usual form of $Cr \cdot H_2O$ supplied commercially. Increased residence in the low pH environment of the stomach could well reduce the availability of creatine from meat due to conversion to creatinine (Edgar and Shriver, 1925).

Creatine supplied in solid form could similarly have a reduced bioavailability, arising, in this case, from its low solubility, again rendering it more susceptible to conversion to creatinine in the stomach. As a result,

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the commercial literature in general recommends that creatine is taken as a drink. This assumed lower bioavailability of creatine supplied in solid form has restricted the introduction of preparations based on the ingestion of solid $Cr \cdot H_2O$ or of $Cr \cdot H_2O$ added directly to food sources.

Our aims were to characterize the absorption of creatine from meat (Study 1), as a natural source of dietary creatine, and when supplied as $Cr \cdot H_2O$ in solid form (Study 2) and to compare absorption in each case to that when creatine is ingested in solution. The assessment of creatine absorption was based upon the changes with time in the plasma concentration curve.

Materials and methods

Study 1: creatine administered in meat or as a solution

Five males aged 24–31 years with a body mass of 75.1 ± 7.8 kg (mean ± *s*) participated in the study. None of them had previously taken creatine as a supplement. For each participant, there were three experimental sessions (A, B and C). The order of sessions was randomized using a Latin square design.

Each participant presented to the laboratory at 08.00 h after an overnight fast. A 19-gauge catheter was inserted into the left or right antecubital vein and was kept patent by flushing with physiological saline. A 2.5 ml blood sample was drawn a few minutes before the participants received the appropriate treatment. In session A, they consumed 300 ml of ambient temperature water over 1–2 min. In session B, they consumed a portion of rump steak weighing 395–426 g from which any visible fat or connective tissue had first been removed. The steak was seasoned and lightly fried in a small amount of fat for 20–30 s on each side to increase acceptability and palatability, while minimizing the breakdown of creatine to creatinine. The participants were asked to consume the steak within 5–10 min and were allowed 300 ml of ambient temperature water to drink. Two 5–10 g samples of each steak were frozen at −30°C for subsequent analysis of creatine and creatinine. In session C, the participants consumed approximately 2.3 g of $Cr \cdot H_2O$ (equivalent to 2 g of creatine) dissolved in 250 ml of 30°C water over 1–2 min. Powder $Cr \cdot H_2O$ (in this and study 2) was supplied by Chemie Linz (Linz, Austria). Residual creatine in the container was washed out using a further 50 ml of ambient temperature water.

Blood samples of 2.5 ml were collected 0.5, 1, 1.5, 2, 3, 4, 5 and 6 h after complete ingestion of the creatine solution or meat using lithium heparin as anticoagulant. Plasma was harvested within 15 min and stored frozen at −30°C.

No food was consumed until after the collection of the final blood sample, although water was allowed (200 ml in any one hour) after the 2 h sample.

Study 2: creatine administered in solid form or as a solution

Five participants (four males, one female) aged 29–34 years with a body mass of 75.6 ± 12.3 kg took part in the study. None had taken creatine in the previous 3 months. For each participant, there were three experimental sessions (D, E and F). The order of sessions was randomized using a Latin square design.

Each participant presented to the laboratory as before and a 2.5 ml blood sample was drawn a few minutes before the administration of the experimental treatment. In sessions D and E, the participants consumed 2.3 g of $Cr \cdot H_2O$ over 1–2 min, in session D dissolved in 250 ml of 30°C water and in session E as a suspension added briefly to 250 ml of ice-cold water. Residual creatine in the container was washed down using 50 ml of ambient temperature or ice-cold water (as appropriate). In session F, the participants were asked to crush and swallow two compressed flavoured lozenges, each containing 1.1–1.2 g $Cr \cdot H_2O$ (Natural Alternatives Inc., San Marcos, CA, USA). Thereafter, the participants were given 300 ml of ambient temperature water.

Blood samples of 2.5 ml were collected and treated as before. No food was consumed until after the collection of the final blood sample, although water was allowed after the 2 h sample.

Analysis of plasma

Study 1. In Study 1, 500 μl of thawed plasma were deproteinized with 15 μl of 70% weight/weight (w/w) perchloric acid ($HClO_4$); 360 μl of the supernatant was neutralized with 90 μl of 2.5 $mol \cdot l^{-1}$ potassium bicarbonate ($KHCO_3$). Creatine was assayed at pH 8.5 in the presence of creatine kinase, pyruvate kinase and lactate dehydrogenase by measurement of the oxidation of nicotinamide adenine dinucleotide (reduced form) (NADH) at 340 nm (Harris *et al.*, 1974). Creatinine was not measured.

Study 2. In Study 2, 250 μl thawed plasma were deproteinized with 125 μl of 1 $mol \cdot l^{-1}$ $HClO_4$. Creatine and creatinine in 200 μl of the acid extract were removed using a C18 solid-phase extraction column and eluted with 400 μl of 400 $mmol \cdot l^{-1}$ sodium dihydrogen phosphate (NaH_2PO_4), pH 2.8. Creatine and creatinine in the eluates were determined by high-performance liquid chromatography (HPLC) using the method of Murakita (1988).

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Analysis of meat and lozenges

For each sample of fried steak, two 100 mg portions were homogenized with 1 ml of water. A 750 μl aliquot of the homogenate was extracted with 22.5 μl of 70% w/w $HClO_4$ and, after centrifugation, were neutralized with 2.5 mol·l^{-1} $KHCO_3$ (2.5 μl for every 100 μl supernatant). Neutralized extracts were assayed for creatine and creatinine by HPLC using the method of Dunnett *et al.* (1991). This method can also detect phosphorylcreatine (in contrast to that of Murakita, 1988), although in practice phosphorylcreatine was not found in any of the samples. The Cr·H_2O content of the lozenges was verified by extracting with water and assaying using the method of Murakita (1988).

Data analysis

The mean area under the plasma creatine concentration curve was calculated using the trapezoidal rule and based on the assumption that, after 6 h, the plasma concentration declined linearly to reach once more the pre-dose concentration at 8 h.

Results

Study 1

The participants consumed an average of 408 g steak with creatine and creatinine contents of 5.41 ± 0.21 and 0.34 ± 0.28 g·kg^{-1}, respectively. The average dose of creatine ingested was 2.20 ± 0.08 g, equivalent to 2.50 g Cr·H_2O and 10.5% higher than planned. In the absence of food, plasma creatine showed no significant change (Fig. 1), averaging 26.4 ($^{1-5}\sigma_w$ = 5.1) μmol·l^{-1} (where $^{1-5}\sigma_w$ = the within-subject standard deviation).

Ingestion of 2 g of creatine in solution caused a rapid increase in peak plasma concentration after 1 h at 287 ± 115 μmol·l^{-1}, followed by a rapid decline (Fig. 1). After meat ingestion, peak plasma concentration was reached later (two participants at 1 h, two at 1.5 h and two at 2 h) and was 182 ± 52.4 μmol·l^{-1}. The fall in the plasma concentration after meat ingestion was similarly delayed relative to the change after ingestion of the same approximate dose as a solution (Fig. 1). The areas under the plasma concentration curve calculated for the 2 g in solution and after meat ingestion were 507 ± 205 and 518 ± 153 μmol·h·l^{-1}, respectively. There was no significant difference ($P > 0.05$) in the area under the plasma creatine concentration curve between the two treatments.

Study 2

Ingestion of 2 g of creatine in solution resulted in a mean peak creatine concentration at 30–60 min of 386 ± 87.7 μmol·l^{-1} (Fig. 2), 30% higher than in Study 1 and reflecting a different group of participants. The mean area under the plasma creatine concentration curve was 622 ± 193 μmol·h·l^{-1} (23% higher than in Study 1). Mean peak concentration was lower after ingestion of the same amount of creatine as a lozenge (277 ± 52.7 μmol·l^{-1}) or suspension (269 ± 66.6 μmol·l^{-1}), although the difference was not significant ($P > 0.05$). Peak concentrations occurred between 1 and 1.5 h. From 2 h onwards, the concentration, after either treatment, declined in parallel with that after the drink (Fig. 2). The areas under the plasma creatine concentration curve after the lozenge and suspension were 438 ± 131 and 399 ± 196 μmol·h·l^{-1}, respectively, or 70.9% and 63.9% of that for the drink. The areas under the plasma creatine concentration curve after the lozenge or suspension were significantly lower ($P < 0.05$) than after 2 g in solution.

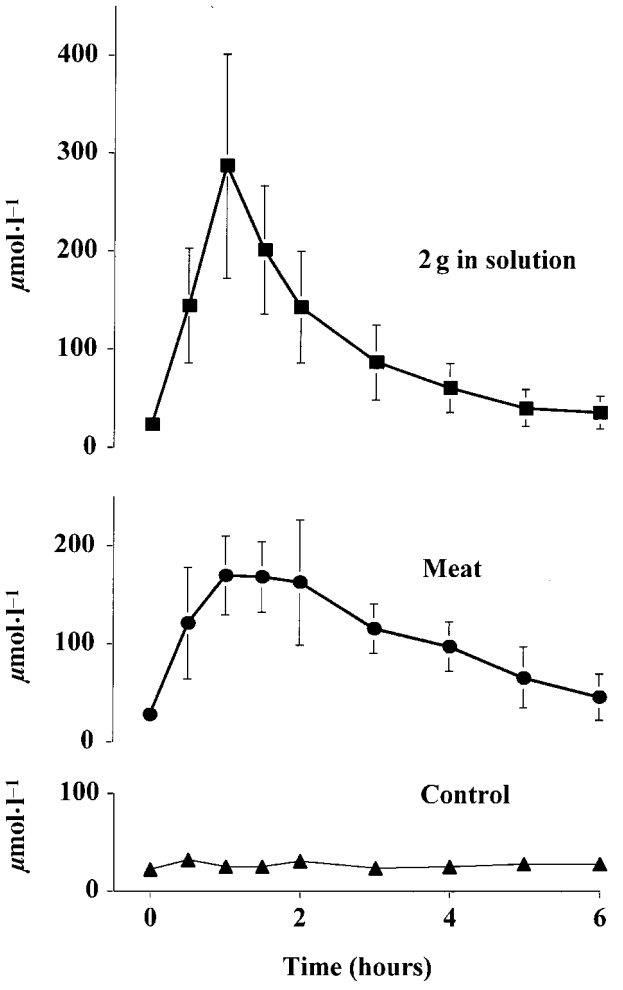

Fig. 1. Mean plasma creatine after the ingestion of water (control), of 2.0 g (equivalent to 2.3 g Cr·H_2O) dissolved in water or an equivalent dose, or 2.2 g (2.5 g Cr·H_2O) after ingestion of 408 g of lightly cooked steak.

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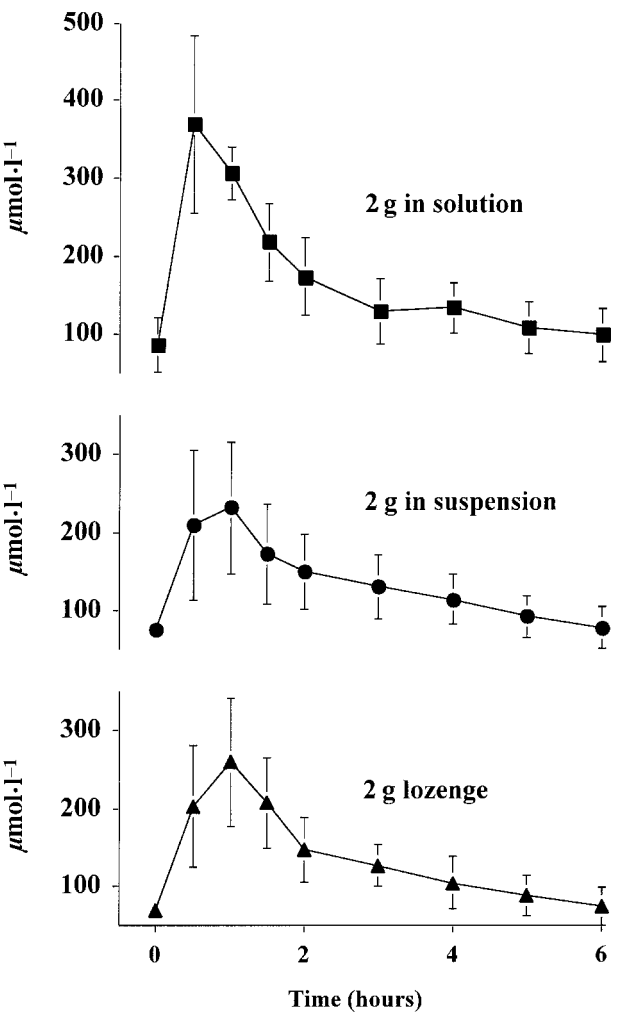

Fig. 2. Mean plasma creatine after the ingestion of 2 g (equivalent to 2.3 g $Cr \cdot H_2O$) in solution, as a crystalline suspension in ice-cold water or divided between two compressed lozenges with added flavouring.

There was no change in the plasma creatinine concentration after the ingestion of the solution, the suspension or lozenges.

Discussion

In Studies 1 and 2, administration of creatine as a drink resulted in a rapid increase in the plasma concentration, in a manner similar to that reported previously (Harris *et al.*, 1992). In contrast, ingestion of approximately the same amount of creatine in meat attenuated the initial response but extended the period over which a concentration close to the peak was attained. Creatine in meat will be in solution but retained within its structure. Release, therefore, is likely to be spread over time. Despite this, and the consequent greater exposure to the low pH in the gastric region, the areas under the plasma creatine concentration curve were approximately the same (and even more so when allowance is made for the slightly higher amount of creatine in the ingested steak), indicating approximate bioequivalence.

It could be argued that the lower increase in plasma creatine after ingestion of the 400 g of steak was the result of increased uptake into muscle due to an increase in circulating insulin, which has been reported to augment creatine retention in muscle (Haughland and Chang, 1975). Green *et al.* (1996) reported increased creatine retention in humans when insulin is increased by co-administration of carbohydrate, resulting in a lower area under the plasma creatine concentration curve for the same ingested dose, but with no increase in urinary excretion. A similar enhancement in muscle creatine uptake was reported by Steenge *et al.* (2000) after the ingestion of sufficient protein and carbohydrate to increase serum insulin to 100 $mU \cdot l^{-1}$. The area under the plasma creatine concentration curve in the present study, however, was the same for both meat and the solution, which would appear to indicate that the effect of the co-ingestion of food was in this case small, if there was one at all.

Meat constitutes the principal dietary source of creatine for humans and carnivorous animals. Although cooking results in some degradation (Macy *et al.*, 1970; Harris *et al.*, 1997), most will be preserved if the cooking time is kept relatively short or if the stock in which the meat is cooked has a pH above 5.5. Although all phosphorylcreatine had apparently been converted to creatine in the steak used, degradation of creatine to creatinine was less than 7% even after frying (although, by intention, the cooking time was kept as short as possible). Only exceptionally is meat consumed on its own and it is possible that the presence of other foods in a mixed meal would alter the time course of creatine absorption from meat and possibly even its bioavailability. These aspects were not examined in the present study.

Dietary intake of creatine is highly variable, ranging from zero in the case of a vegetarian to as high as 15 g or more in a 75 kg human consuming only meat (e.g. the traditional Inuit diet and that of other peoples living north of the Arctic circle; Vaughan, 1999). Hoogwerf *et al.* (1986) estimated that the 'average' American diet contains 200 g of meat, sufficient to provide approximately 1 g of dietary creatine. However, estimates of meat ingestion in north European prehistoric man (Tannabill, 1988) would indicate a higher dietary intake of 3–6 g of creatine per day (equivalent to 3.5–7.0 $g \cdot day^{-1}$ of the monohydrate), representing the dietary intake of adults for much of the evolution of *Homo sapiens*.

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Peak concentrations with either the lozenge or suspension tended to be lower than for the same dose administered as a solution, but there was no extension of the period in which the concentration was maintained close to its peak. In the case of the suspension, it is possible that uptake may have been delayed by the use of 300 ml of ice-cold water. However, the similarity in plasma concentrations and areas under the curve for both the lozenge and suspension would suggest that any such effect was small. The significantly lower estimates of the area under the plasma creatine concentration curve obtained with either the suspension or lozenge, compared to the solution, suggests a lower bioavailability of creatine when supplied in solid form. Despite this, there was no evidence of any increase in creatinine that might indicate increased degradation. Our results suggest that, to obtain the same peak plasma concentration, 20% or more $Cr \cdot H_2O$ in crystalline form would have to be consumed, although 2.3 g was still sufficient to raise the concentration five- to six-fold.

In conclusion, creatine administered as meat or in solid form is readily absorbed but may lead to lower peak concentrations. In the case of meat, this is compensated for by an extension to the period over which the concentration is maintained close to its peak.

Acknowledgement

The authors are grateful to Natural Alternatives International of San Marcos, California, USA, for their financial support and for providing compressed lozenges of creatine monohydrate and other materials used in the study.

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