Original Paper

Annals of Nutrition & Metabolism

Ann Nutr Metab 2003;47:11–15
DOI: 10.1159/000068908

Received: March 26, 2002
Accepted: June 21, 2002

Creatine Supplementation Affects Glucose Homeostasis but Not Insulin Secretion in Humans

Kieron B. Rooney Janet M. Bryson Alison L. Digney Caroline D. Rae
Campbell H. Thompson

Human Nutrition Unit, School of Molecular and Microbial Biosciences, University of Sydney, Australia

Key Words
Creatine · Glucose · Insulin · Vegetarians · Hyperglycaemia

Abstract
Aims: In this study, it was investigated whether the glucose homeostasis is affected by dietary creatine supplementation. For this purpose, the plasma glucose concentration and the plasma insulin response to an oral glucose load were measured in creatine-supplemented vegetarians. ***Methods:*** The subjects were supplemented with either 5 g of creatine monohydrate (creatine-treated group, CREAT) or 5 g of maltodextrin (control group, CON) per day for 42 days. On days 0 and 43, blood samples were collected before as well as 10, 20, and 30 min following an oral glucose load and analyzed for plasma creatine, insulin, and glucose levels. ***Results:*** Creatine supplementation resulted in an increase in plasma creatine (CREAT 92.7 ± 14.6 μ*M* vs. CON 31.2 ± 3.2 μ*M;* p = 0.001). There was a trend (p = 0.07) towards elevated fasting plasma glucose levels following creatine supplementation, while the plasma glucose response to the glucose load was enhanced (CREAT 168.2 ± 5.3 m*M* · min vs. CON 129.6 ± 14.7 m*M* · min; p = 0.05). There was no difference observed in the plasma insulin response to the glucose load between the groups. ***Conclusion:*** This study shows that creatine supplementation may result in abnormalities in glucose homeostasis in the absence of changes in insulin secretion.

Introduction

Creatine can be stored in skeletal muscle as phosphocreatine, where it acts as a buffer for adenosine triphosphate levels within the muscle cytosol at the beginning and at the end of exercise [1]. Although the skeletal muscle is the major reservoir for creatine and phosphocreatine in the body, dietary supplementation has resulted in increased total creatine stores in a number of other tissues such as brain [2], pancreas [3], and heart and kidney [4].

Evidence of an influence of dietary creatine supplementation upon the carbohydrate metabolism is accumulating. In humans, a single oral dose of creatine significantly decreased the plasma glucose levels in an insulin-dependent diabetic population over a 2-hour period [5].

KARGER

Fax + 41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

0250–6807/03/0471–0011$19.50/0

Accessible online at:
www.karger.com/anm

Mr. Kieron Rooney
Human Nutrition Unit, School of Molecular and Microbial Biosciences
Building G08, University of Sydney
Sydney, NSW 2006 (Australia)
Tel. +61 2 9351 3620, Fax +61 2 9351 6022, E-Mail kroo4366@mail.usyd.edu.au

Furthermore, dietary creatine supplementation has been shown to increase the resting muscle glycogen stores [6] as well as to increase glycogen resynthesis rates [7] and glucose transporter protein levels (GLUT4) [8] in skeletal muscle following exercise.

It, therefore, appears that creatine supplementation may enhance skeletal muscle glucose uptake and glycogen synthesis [8]. However, this was not observed following 5 days of dietary creatine supplementation in rats [6].

The basis of these effects of creatine supplementation on the glucose metabolism may be a relationship between creatine and pancreatic insulin secretions as opposed to a direct relationship between creatine and muscle glucose handling.

In vitro studies have shown that creatine directly stimulates the insulin secretion from the pancreas [9, 10]. Creatine supplementation in rats for 5 days showed no change in fasting plasma insulin or plasma insulin levels 1 h after feeding [6]. The plasma insulin concentration was not altered by either a single 5-gram dose of creatine [11] or following 3 days of creatine supplementation in humans [12]. However, since athletes often take creatine for periods exceeding 3 days, these short-term studies on insulin secretion may be inadequate.

In a recent paper [3], we have shown that long-term creatine supplementation in rats alters the insulin secretion in vivo, and this could provide a mechanism for the observed effects on glucose homeostasis and glycogen storage in skeletal muscle observed with creatine supplementation. The aim of this study was to investigate the effects of long-term dietary creatine supplementation on both plasma glucose and insulin responses to an oral glucose load in a human vegetarian population.

The increase in tissue creatine content observed in supplemented individuals is dependent upon the initial tissue creatine content [13], such that a low initial muscle creatine content results in increased levels of muscle creatine retention following supplementation. Vegetarians have lower baseline tissue creatine levels. The effect of creatine supplementation on the tissue creatine levels in vegetarians is, therefore, likely to be greater than in omnivores, giving a larger effect size.

Subjects and Methods

Fourteen healthy vegetarians volunteered to take part in the study. They were randomly divided into two groups of 7. This study complied with ethical guidelines laid down for human research by the Australian NHMRC and was approved by the University of Sydney Human Research Ethics Committee. Before taking part in the study, all subjects were made aware of the experimental procedures involved and gave their voluntary, written consent to take part.

All subjects reported to the laboratory on the morning of days 0 and day 43 of the study between 07.30 and 09.30 h in a fasted state having abstained from food for no less than 10 h. Height and weight were measured, and a fasting blood sample was collected through a venous cannula that had been inserted into the arm. The subjects then drank 75 g of glucose (Glucodin) in a total volume of 200 ml within 2 min. Further 4-ml blood samples were collected into lithium-heparin-coated tubes from the venous cannula 10, 20, and 30 min following commencement of the drink. The blood samples were centrifuged, and plasma was removed and stored at –80°C until analysis for glucose and insulin concentrations. The plasma glucose and insulin responses were assessed by the total area under the curve (TAUC) for values obtained over the 30 min. Fasting blood samples were also analyzed for creatine as well as glucose and insulin levels.

Following the visit on day 0, the subjects were given 46 vials containing 5 g of either creatine monohydrate powder (Pan Pharmaceuticals, Moorebank, Australia; creatine-treated group, CREAT; n = 7, 1 male, 6 females) or 5 g of a placebo (maltodextrin powder; Manildra Starches, Auburn, Australia; control group, CON; n = 7, 3 males, 4 females). The subjects were asked to maintain their normal diet and physical activity routine throughout the protocol. On completion of the study, the subjects were asked to return the remaining vials, and the number remaining was used as a measure of compliance.

Plasma glucose was analyzed using a spectrophotometric glucose oxidase method. Plasma insulin was measured using a specific double antibody radio-immunoassay (Linco Research, St. Charles, Mo., USA). Plasma creatine, measured from perchloric acid extracts using a fluorometric assay [14], was used as an alternate measure of compliance.

Statistical significance was determined using an unpaired Student t test for comparison between CON and CREAT groups for all experiments or a paired Student t test for comparison within groups between pre- and post-supplementation data. Statistical significance was inferred if $p < 0.05$.

Results

As compared with the measurements before supplementation, the subjects in the CREAT group showed a significant increase in body weight ($p = 0.0004$, table 1). No change was observed in the CON group. Despite the weight increase in the CREAT group, the body weight was similar between CREAT and CON groups before and after supplementation (table 1).

Dietary creatine supplementation significantly elevated the plasma total creatine concentration when compared to the CON group or the CREAT group on day 0 (table 1). On day 43, the plasma creatine level was unchanged in the CON group when compared to day 0.

The fasting plasma glucose levels were elevated, but not significantly so, in the CREAT group as compared with the values before supplementation (day 0: 4.2 ±

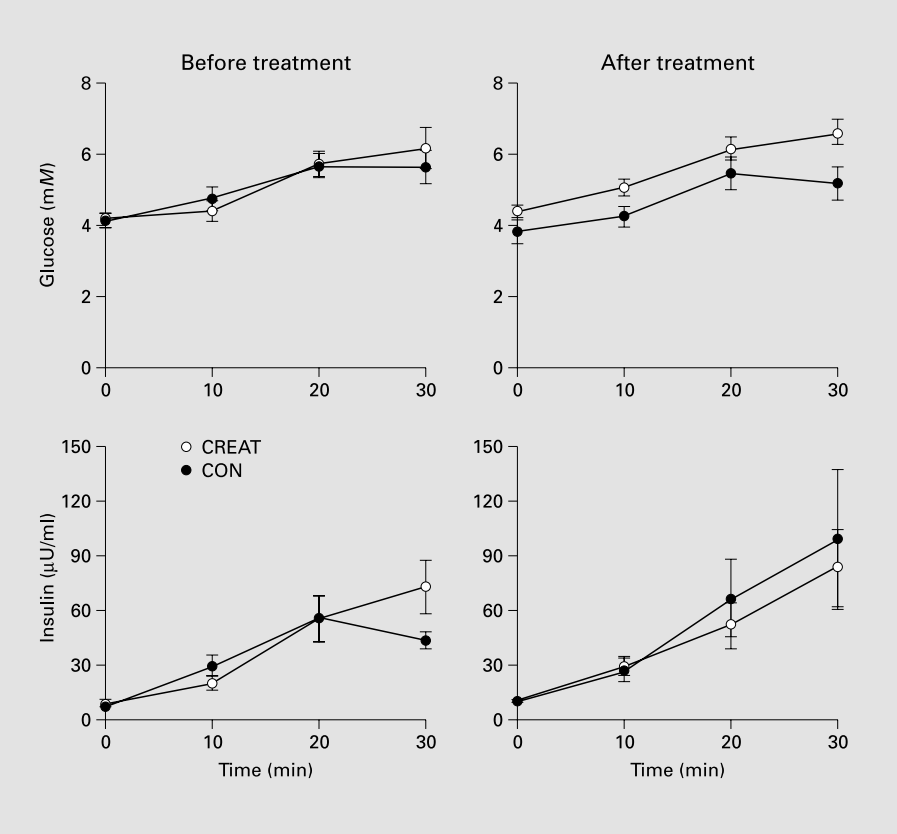

Fig. 1. Plasma glucose responses (upper panels) and plasma insulin responses (lower panels) of vegetarians given an oral glucose load before and after 42 days of dietary creatine supplementation (open diamonds) or placebo supplementation (filled diamonds). Data are expressed as mean values ± SEM.

Table 1. Body weight and creatine levels in both treatment groups (mean ± SEM)

	CREAT group		CON group	
	day 0	day 43	day 0	day 43
Body weight, kg	69.5 ± 5.0	71.3 ± 5.2*	66.0 ± 3.3	66.5 ± 3.8
Plasma creatine, µ*M*	34.8 ± 5.2	92.7 ± 14.6*,†	31.3 ± 2.8	31.2 ± 3.2

* $p < 0.01$ (paired Student's t test) day 0 vs. day 43 CREAT group.
† $p < 0.001$ (unpaired Student's t test) day 43 CREAT group vs. day 43 CON group.

0.1 m*M,* day 43: 4.4 ± 0.2 m*M*, p = 0.07). The plasma glucose TAUC values were similar between both groups before supplementation (fig. 1). On day 43, there was a significant increase (p = 0.05) in the plasma glucose response for the CREAT group as compared with the CON group (fig. 1) which was mostly due to the elevation of the fasting glucose concentration. The increase in glucose TAUC values between pre- and post-treatment values was not significant (p = 0.06) for the CREAT group.

After 42 days, the fasting plasma insulin concentration was not changed in the CREAT group. The plasma insulin response was similar between CON and CREAT groups both before and after supplementation (fig. 1).

Discussion

The novel finding of this study is that, as compared with the placebo-supplemented controls, creatine supplementation caused an increased plasma glucose response to an oral glucose load. No creatine-induced differences in either fasting plasma insulin or plasma insulin response to an oral glucose load were observed. Plasma creatine and body weight were increased by 42 days of dietary creatine supplementation.

The potential for creatine and creatine-like substances to be used as possible tools in the regulation of glucose homeostasis has been recognized since Hill [15] induced a hypoglycaemic response in dogs in vivo following an injection of creatine. More recently, the observation of a hypoglycaemic response to an oral creatine load in insulin-dependent diabetics in the absence of any changes in insulin [5] suggested that creatine may be directly influencing glucose utilization at the peripheral target cells. In that study, no effect of a single dose of creatine on the blood glucose levels in their control subjects was observed. In our study, in which creatine was given for 42 days, a hyperglycaemic effect of creatine supplementation in response to an oral glucose load was observed. To our knowledge, no other studies have investigated this effect of creatine supplementation in humans. In rats, the plasma glucose response to a chow meal after 5 days of creatine supplementation was unchanged [6]. Elevated plasma glucose levels were observed, however, following an oral glucose load in rats supplemented with creatine for 8 weeks [3], supporting the findings of the current study. Thus, longer periods of creatine supplementation may be required to observe changes in glucose homeostasis in otherwise healthy individuals.

The hypoglycaemic effect of creatine on plasma glucose may only be present in those with an impaired insulin secretion [5]. Long-term creatine supplementation in rats has been shown to increase the insulin secretion in response to an oral glucose load as well as to alter glucose homeostasis [3]. The change in insulin following creatine supplementation was seen to follow an increase in the pancreatic total creatine content which may have altered insulin secretory processes. In humans, the effect of dietary creatine supplementation on insulin is less well examined, with pancreatic creatine assessment in vivo not yet possible. Abnormal hyperinsulinaemia following creatine alone [5, 11] or creatine and glucose ingestion combined [12] has not been seen in vivo in human studies. The present study, which incorporated a longer period of creatine supplementation, supports results of earlier studies suggesting that creatine or creatine supplementation does not have an effect on the insulin secretion in vivo in humans.

The present study investigated a vegetarian population. While the plasma creatine concentration was significantly elevated in creatine-supplemented subjects in the present study, the low initial tissue creatine content and the slow creatine turnover rate in vegetarians [16] might have resulted in the muscle absorbing the supplementary creatine such that other tissues, like the pancreas, were not influenced by the additional creatine in the diet. Furthermore, the present study investigated a mixed population of males and females. Many creatine supplementation studies have used mixed populations previously, and it is generally accepted that there are no gender differences in the response to creatine supplementation [17].

In conclusion, the present study has shown that the plasma glucose response to an oral glucose load was elevated after 42 days of creatine supplementation in humans. The changes in glucose TAUC values were not proportional to the increase in plasma creatine levels observed. Furthermore, these changes in plasma glucose were seen in the absence of any changes in plasma insulin. Long-term creatine supplementation in humans alters glucose homeostasis independent of changes in insulin secretion.

Acknowledgment

This work was supported with a grant from the National Health and Medical Research Council of Australia which included a fellowship for C.D. Rae.

References

1 Casey A, Constantin-Teodosiu D, Howell S, Hultman E, Greenhaff PL: Creatine ingestion favorably affects performance and muscle metabolism during maximal exercise in humans. Am J Physiol 1996;271:E31–E37.

2 Stockler S, Holzbach U, Hanefeld F, Marquardt I, Helms G, Requart M, Hanicke W, Frahm J: Creatine deficiency in the brain: A new, treatable inborn error of metabolism. Pediatr Res 1994;36:409–413.

3 Rooney K, Bryson J, Phuyal J, Denyer G, Caterson I, Thompson C: Creatine supplementation alters insulin secretion and glucose homeostasis in vivo. Metabolism 2002;51:518–522.

4 Horn M, Frantz S, Remkes H, Laser A, Urban B, Mettenleiter A, Schnackerz K, Neubauer S: Effects of chronic dietary creatine feeding on cardiac energy metabolism and on creatine content in heart, skeletal muscle, brain, liver and kidney. J Mol Cell Cardiol 1998;30:277–284.

5 Rocic B, Vucic M, Mesic R, Rocic P, Coce F: Hypoglycemic effect of creatine in insulin dependent diabetic patients. Diabetol Croatica 1995;24:117–120.

6 Op't Eijnde B, Richter EA, Henquin JC, Kiens B, Hespel P: Effect of creatine supplementation on creatine and glycogen content in rat skeletal muscle. Acta Physiol Scand 2001;171:169–176.

7 Robinson TM, Sewell DA, Hultman E, Greenhaff PL: Role of submaximal exercise in promoting creatine and glycogen accumulation in human skeletal muscle. J Appl Physiol 1999; 87:598–604.

8 Op't Eijnde B, Urso B, Richter EA, Greenhaff PL, Hespel P: Effect of oral creatine supplementation on human muscle GLUT4 protein content after immobilization. Diabetes 2001; 50:18–23.

9 Alsever RN, Georg RH, Sussman KE: Stimulation of insulin secretion by guanidinoacetic acid and other guanidine derivatives. Endocrinology 1970;86:332–336.

10 Marco J, Calle C, Hedo JA, Villanueva ML: Glucagon-releasing activity of guanidine compounds in mouse pancreatic islets. FEBS Lett 1976;64:52–54.

11 Green AL, Hultman E, Macdonald IA, Sewell DA, Greenhaff PL: Carbohydrate ingestion augments skeletal muscle creatine accumulation during creatine supplementation in humans. Am J Physiol 1996;271:E821–E826.

12 Green AL, Simpson EJ, Littlewood JJ, Macdonald IA, Greenhaff PL: Carbohydrate ingestion augments creatine retention during creatine feeding in humans. Acta Physiol Scand 1996;158:195–202.

13 Harris RC, Soderlund K, Hultman E: Elevation of creatine in resting and exercised muscle of normal subjects by creatine supplementation. Clin Sci (Colch) 1992;83:367–374.

14 Conn RB: Fluorimetric determination of creatine. Clin Chem 1960;6:537–548.

15 Hill R: The effect of the administration of creatine on the blood sugar (abstract). J Biol Chem 1928;78:iv.

16 Delanghe J, De Slypere JP, De Buyzere M, Robbrecht J, Wieme R, Vermeulen A: Normal reference values for creatine, creatinine and carnitine are lower in vegetarians. Clin Chem 1989;35:1802–1803.

17 Terjung RL, Clarkson P, Eichner ER, Greenhaff PL, Hespel PJ, Israel RG, Kraemer WJ, Meyer RA, Spriet LL, Tarnopolsky MA, Wagenmakers AJ, Williams MH: American College of Sports Medicine Roundtable: The physiological and health effects of oral creatine supplementation. Med Sci Sports Exerc 2000;32: 706–717.