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Effects of creatine supplementation on glucose tolerance and insulin sensitivity in sedentary healthy males undergoing aerobic training

B. Gualano, R. B. Novaes, G. G. Artioli, T. O. Freire, D. F. Coelho, F. B. Scagliusi, P. S. Rogeri, H. Roschel, C. Ugrinowitsch, and **A. H. Lancha Junior**

Laboratory of Applied Nutrition and Metabolism, Physical Education and Sport School, University of São Paulo, São Paulo, Brazil

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Summary. Recent findings have indicated that creatine supplementation may affect glucose metabolism. This study aimed to examine the effects of creatine supplementation, combined with aerobic training, on glucose tolerance in sedentary healthy male. Subjects ($n = 22$) were randomly divided in two groups and were allocated to receive treatment with either creatine (CT) ($\sim 10\,g \cdot day$ over three months) or placebo (PT) (dextrose). Administration of treatments was double blind. Both groups underwent moderate aerobic training. An oral glucose tolerance test (OGTT) was performed and both fasting plasma insulin and the *homeostasis model assessment* (HOMA) *index* were assessed at the start, and after four, eight and twelve weeks. CT demonstrated significant decrease in OGTT area under the curve compared to PT ($P = 0.034$). There were no differences between groups or over time in fasting insulin or HOMA. The results suggest that creatine supplementation, combined with aerobic training, can improve glucose tolerance but does not affect insulin sensitivity, and may warrant further investigation with diabetic subjects.

Keywords: Creatine – Glucose tolerance – Insulin sensitivity – Aerobic training

Introduction

Creatine is a natural amine found in fish, and, red and white meats. It is synthesized endogenously by a two-step mechanism involving L-arginine: glycine amidinotransferase (AGAT) and S-adenosyl-L-methionine: N-guanidinoacetate methyltransferase (GAMT). AGAT is predominantly expressed in kidney and pancreas, and GAMT is mainly localized in liver and pancreas.

Several studies have focused on the ergogenic capacity of creatine loading since Harris et al. (1992) demonstrated in humans its efficacy to increase the skeletal muscle creatine content. In addition, some authors have indicated that creatine supplementation may also improve glucose metabolism. It has been repeatedly demonstrated that creatine supplementation can augment muscle glycogen accumulation in humans (Green et al., 1996; Robinson et al., 1999; van Loon et al., 2004) and rats (Einjde et al., 2001a). Additionally, Eijnde et al. (2001b) showed that creatine supplementation offsets the decline in muscle GLUT-4 expression after 2 weeks of immobilization and increases GLUT-4 content during subsequent rehabilitation training in healthy males. Furthermore, Ferrante et al. (2000) suggested that creatine intake can ameliorate hyperglycaemia, typical of transgenic Huntington disease mice, delaying the onset of diabetes. Supporting these findings, Eijnde et al. (2006) verified that creatine ingestion can reduce the insulinogenic index in an animal model of inherited type 2 diabetes. Based on the above data, it has been hypothesised that oral creatine supplementation may improve glucose uptake and may have therapeutic potential in the prevention/treatment of non-insulin-dependent-diabetes mellitus (Eijnde et al., 2001b). However, the direct effects of creatine supplementation on glucose tolerance have not been investigated in detail. For instance Newman et al. (2003) demonstrated that creatine supplementation for 28 days did not affect glucose tolerance in healthy males, but the chronic effects of supplementation were not investigated.

A further controversial point is whether creatine supplementation affects insulin secretion. Earlier studies in vitro suggested that there was a modest stimulation of insulin secretion by supra physiological creatine concentrations in both perfused rat pancreas (Alsever et al., 1970) and incubated mouse islets (Marco et al., 1976). In addition, Rooney et al. (2002) observed that prolonged

creatine supplementation elevated both insulin and glycaemia in rats. However, studies in humans have failed in mimicking any such creatine-induced hyperinsulinemia (Newman et al., 2003; van Loon et al., 2004). We considered it important, therefore, to investigate if long-term creatine supplementation affected glucose metabolism by improving peripheral insulin sensitivity or by promoting insulin hypersecretion.

Moreover, it is well documented that aerobic training can improve glucose tolerance and enhance skeletal muscle sensitivity to insulin (Ferrara et al., 2006; Sriwijitkamol et al., 2006; for details and mechanisms, see Pereira and Lancha, 2004). Thus, we hypothesized that long term creatine supplementation, combined with aerobic training, may produce an additive effect on glucose uptake in humans. The purpose of this study was to investigate the effects of creatine supplementation on glucose tolerance and insulin sensitivity in sedentary healthy males submitted to moderate intensity aerobic training.

Materials and methods

Subjects

Twenty-two males without pre-existing diseases, who had lead a predominately sedentary life for at least five years, were eutrophic and not vegetarian, were select by personal interview and then randomly allocated into two treatment groups. Subject details are given in Table 1.

The study was approved by the Ethics and Research Committee of the School of Physical Education and Sport, Sao Paulo University. Subjects were informed of the experimental procedures and possible risks before their informed written consent to participate was obtained.

Experimental protocol

Subjects were randomly assigned to receive either treatment with creatine (CT; $n = 12$) or placebo group (PT; $n = 10$). Treatment allocation was double-blind. Both groups were submitted to moderate intensity aerobic training for three months. Prior to training (Pre), after 4 (Post 4), 8 (Post 8) and 12 weeks (Post 12), an oral glucose tolerance test (OGTT) was performed, and fasting plasma insulin and fasting plasma glucose were determined and used to estimate *homeostasis model assessment* (HOMA) *index*. Blood samples were obtained from an antecubital vein, following a 12 h overnight fast, 48 h after the last training session and at all time points during the OGTT. Possible differences between groups, and changes during treatment, in dietary intake were assessed by 24 h dietary recall at baseline and Post 12.

Table 1. Subject characteristics in CT ($n = 12$) and PT ($n = 10$) groups

	CT group	PT group
Age (years)	24.4 ± 5.0	24.2 ± 4.2
BMI ($kg \cdot m^{-2}$)	23.2 ± 4.6	24.1 ± 3.8
Body Fat Content (%)	17.3 ± 4.1	17.6 ± 3.8
Waist-to-hip ratio (cm)	0.84 ± 0.06	0.83 ± 0.08
Waist circumference (cm)	81.1 ± 8.8	78.3 ± 10
VO_{2max} ($ml \cdot kg^{-1} \cdot min^{-1}$)	34.6 ± 6.6	35.3 ± 4.3
VT ($ml \cdot kg^{-1} \cdot min^{-1}$)	32.7 ± 6.2	28.9 ± 5.9
Resting HR ($beats \cdot min^{-1}$)	66.0 ± 6.2	65.8 ± 7.5

No significant differences were observed between groups (unpaired *t*-test)
VT Ventilatory gas exchange threshold; *HR* heart rate

Creatine supplementation

The CT group received $0.3\,g \cdot day^{-1} \cdot kg^{-1}$ of body weight for the first week, and $0.15\,g \cdot day^{-1} \cdot kg^{-1}$ of body weight for the next 11 weeks; the PT group was given dextrose in place of creatine, at the same dose. During the loading phase supplements were presented in four packages, with equal content, and subjects were instructed to ingest one supplement package at breakfast, lunch and dinner and the fourth at 10 pm. During the maintenance phase, subjects consumed the supplement during lunch and dinner. All subjects were instructed to dissolve the supplements, preferably in juice, in order to mask both the low solubility of creatine and the taste of dextrose. The compliance to creatine supplementation was monitored weekly by personal communication. The subjects completed a weekly questionnaire regarding possible adverse effects of creatine supplementation (adapted of Volek et al., 2000).

In order to verify the purity of the creatine used, a sample was analysed by HPLC (Zwang and Blijemberg, 1991) and 99.9% purity was established.

VO_{2max} test

VO_{2max} was determined using an incremental treadmill exercise test conducted according to the Bruce protocol. This test is conducted in 3 min stages. The Bruce protocol begins with a speed of $2.74\,km \cdot hour^{-1}$ and a slope of 10% corresponding to a work rate of approximately 4.6 METS. Each 3 min the workload is increased by a combination of increasing the speed and the grade of the treadmill. Attainment of VO_{2max} was accepted when two of three criteria were met: a plateau in VO_2, a respiratory exchange ratio (RER) >1.1 and volitional exhaustion. Ventilatory gas exchange threshold (VT) was determined by the V-slope method (Beaver et al., 1986).

Exercise training

Both groups were submitted to aerobic training, three times a week, for 40 min per session, for 3 months. Running intensity was set at the corresponding heart rate of 70% of VO_{2peak} determined by an incremental VO_{2peak} test. Subjects were requested to run at the pre-set heart rate during the whole training period. Thus an increase in both running distance and intensity were expected as training progressed. All sessions were monitored by a fitness-professional. From the outset it was ruled that subjects would be dropped from the study if they missed three non-consecutives training sessions, or two consecutives sessions. One subject from PT group was excluded for this reason.

Food intake assessment

Food intake was assessed by a 24 h dietary recall, using visual-aid photographs of real foods (Hess, 1997). Energy and macronutrient intakes were analyzed by the Brazilian software, Virtual Nutri (Philippi et al., 1996), based on the Handbook No. 8 (USDA Human Nutrition Information Service: Composition of food. Raw, processed, prepared. Series 1–16. Revised 1976–1986). Additional information was obtained from the Brazilian Table of Food Composition (version 1.0, 1997, University of São Paulo, São Paulo, SP, available on-line: < http://www.fcf.usp.br/tabela >). When data from particular foods were lacking, data from a related food was used.

Glucose tolerance

A catheter was inserted in to an antecubital vein and blood was drawn for analysis of plasma glucose during the OGTT. Subjects ingested a glucose solution [75 g (250 ml water)] and subsequent blood samples were drawn at 30, 60, 90 and 120 min, and centrifuged immediately. Plasma glucose was measured at the same time of collection using a colourimetric enzymatic method based on glucose oxidase. The area under the *plasma glucose* concentration curve (AUC) was calculated by the trapezoidal rule.

Insulin sensitivity

Fasting plasma insulin was measured using a human specific radioimmunoassay kit (Diasorin, Biomedica). *Homeostasis model assessement* (HOMA) *index* was assessed from both the fasting plasma insulin and glucose concentrations, according to Matthews et al. (1985).

Statistical analysis

HOMA, plasma glucose concentration and fasting insulin were tested by Mixed Model ANOVA. Group (creatine and placebo) and time (pre, post 4, post 8, and post 12) were considered as fixed factors and subjects were defined as a random factor. A post-hoc test, with an adjustment by Tukey, was used for multi-comparison purposes.

A random coefficient growth curve model was fitted to the area under the plasma glucose concentration curve (AUC) data in an attempt to determine if experimental and control groups had similar glucose tolerance in the pretest. This model was used due to the fact that it accommodates non-constant correlation between measurements than regular repeated measures ANOVA, and provides a better fit of the AUC data. In addition, this model tested if there was a time trend to a decreased glucose tolerance and if this trend was different between groups (Ugrinowitsch et al., 2004; Littell et al., 2000). One degree of freedom contrast was used for post-hoc comparison purposes. Significance was set at $p < 0.05$. All samples were analyzed in duplicate and the mean value was used for further analysis. Data are presented as mean ± SD.

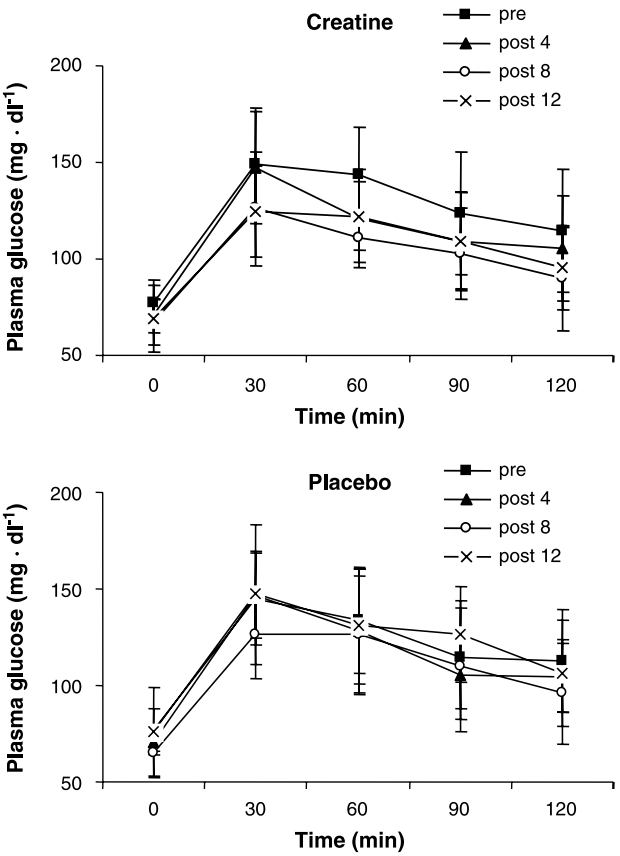

Fig. 1. Main plasma glucose concentration from OGTT test in Creatine group (CT; $n = 12$) and Placebo group (PT; $n = 10$), at baseline and after 4, 8 and 12 weeks. No significant differences were found

Results

There were no differences between or within groups in both nutrient and energy intake (Table 2). Hence, the findings of this study cannot be due differences in trace amounts creatine in the diet or alterations in dietary intake.

Despite high dose of creatine ingested (compared with ACSM recommendation in 2000), there were no reports of any deleterious effects assessed through subjective questionnaire.

Table 2. Food intake by subjects in the CT ($n = 12$) and PT ($n = 10$) groups, assessed by 24 h dietary recall at baseline and after 12 weeks

	CT		PT	
	Pre	Post 12	Pre	Post 12
Energy (kcal)	2728 ± 238	2833 ± 201	2844 ± 201	2899 ± 287
Protein (%)	28.0 ± 4.3	30.0 ± 3.1	29.8 ± 0.3	31.1 ± 3.9
Lipid (%)	25.5 ± 4.9	24.5 ± 4.5	24.9 ± 4.1	26.0 ± 3.1
Carbohydrate (%)	46.3 ± 3.9	43.3 ± 5.3	45.3 ± 4.9	42.9 ± 5.1
Protein/body weight ($g \cdot kg^{-1}$)	1.1 ± 0.3	1.2 ± 0.3	1.0 ± 0.2	1.2 ± 0.3

No significant differences were observed

Figure 1 shows the plasma glucose concentrations for both groups at 0, 30, 60, 90 and 120 min of OGTT test, at baseline and after 4, 8 and 12 weeks. Although CT showed a greater decrease in the glucose curve throughout the experimental period, when compared to PT, neither treatment-by-time interaction nor main effects were oberved.

Figure 2 presents the mean estimates of AUC, as a measure of glucose tolerance, obtained from the OGTT tests. Random coefficient growth curve analysis of the data revealed that there was no difference in the initial AUC values of glucose tolerance between groups ($P = 0.37$). On the other hand, glucose AUC decreased significantly during the training period for both groups ($P = 0.005$), but the rate of decrement was greatest in the CT group ($P = 0.034$). The difference in the rate of decrement in AUC between groups was $-814.3\,mg \cdot dl^{-1} \cdot min^{-1}$ every four weeks. In all periods the CT group demonstrated greater decrease in AUC than the PT group, when compared to baseline (CT – Post 4: $-11 \pm 1\%$; Post 8:

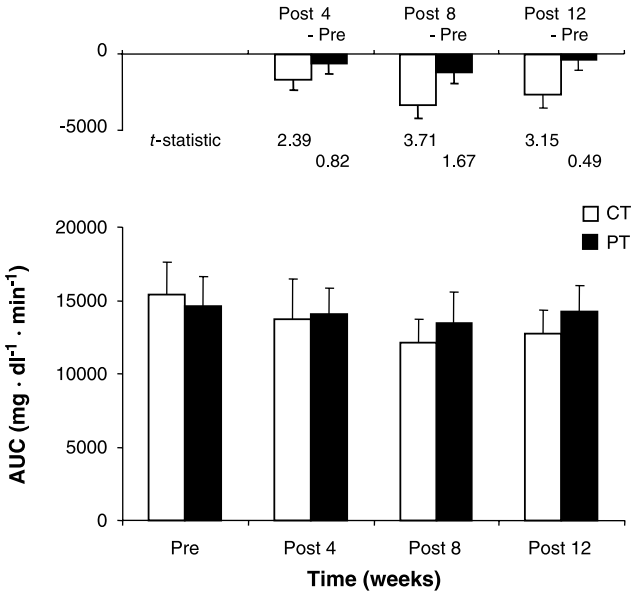

Fig. 2. Bottom: Mean (SD) glucose tolerance estimated from the area under the plasma glucose concentration curve (AUC) obtained in the OGTT test, after 0, 4, 8 and 12 weeks treatment. A random coefficient growth curve analysis revealed decreases in AUC in both groups ($P = 0.005$). However, the rate of decrement in the CT group was greater ($P = 0.034$) than in the PT group. $n = 12$ in CT group and $n = 10$ in PT group. Top: mean (SE) within-subject difference between AUC at each time point and Pre. The *t*-statistic (mean/SE) for each time point is shown, too

Table 3. HOMA and fasting insulin ($\mu U \cdot ml^{-1}$) at 0, 4, 8 and 12 weeks in CT ($n = 12$) and PT ($n = 10$) groups

	Pre	Post 4	Post 8	Post 12
HOMA				
CT	2.47 ± 1.36	2.68 ± 0.61	2.71 ± 1.06	2.13 ± 1.07
PT	2.14 ± 0.59	2.11 ± 0.64	2.48 ± 0.90	2.58 ± 1.53
Fasting insulin				
CT	11.96 ± 5.95	13.89 ± 7.39	15.66 ± 4.54	15.32 ± 6.17
PT	13.54 ± 6.87	12.57 ± 3.76	14.43 ± 4.77	14.59 ± 8.32

No significant differences were observed

$-22 \pm 2\%$; Post 12: $-18 \pm 2\%$ vs. PL – Post 4: $-4 \pm 0.8\%$; Post 8: $-8 \pm 1\%$; Post 12: $-2 \pm 0.7\%$).

HOMA index and fasting insulin did not differ between groups or with time (Table 3).

Discussion

The aim of this was to investigate the effects of creatine supplementation on glucose tolerance and insulin sensitivity in sedentary healthy males submitted to aerobic training.

The scientific literature presents divergent results regarding the effects of creatine supplementation on carbohydrate metabolism. Eijnde et al. (2001b) showed that creatine intake increases GLUT-4 protein content and glycogen accumulation during muscle disuse and a subsequent period of training. The authors pointed out the potential of long term creatine supplementation to prevent or to treat diseases characterized by peripheral insulin resistance. Accordingly, recent findings have demonstrated that creatine supplementation lowers the insulinogenic index both before and after administration of exogenous D-glucose in Goto-Kakizaki rats, a current model of inherited type 2 diabetes (Einde et al., 2006). The authors asserted that this result can be attributable mainly to a lowering in the plasma insulin concentration. On the other hand, Newman et al. (2003) were unable to verify alterations in glucose tolerance after 28 days creatine supplementation ($20\,g \cdot day^{-1}$ during 5 days and $3\,g \cdot day^{-1}$ for the remaining 23 days) in healthy but not exercised subjects. In addition Rooney et al. (2002) suggested that creatine supplementation may induce both abnormalities in insulin metabolism and hyperglycemia in rats.

Our results are in contrast with those of Newman et al. (2003) and Rooney et al. (2002). Several factors may have contributed to the discrepancy between findings. Subjects were supplemented with approximately $20\,g \cdot day^{-1}$ during 7 days followed by $10\,g \cdot day^{-1}$ for a further 11 weeks. This supplementation regimen was substantially greater, both in dose and duration, than the one used by Newman et al. (2003). In the latter study, neither muscle phosphorylcreatine nor total creatine showed any substantial increase with treatment. Hence, the differences in the creatine supplementation protocol (i.e. twofold greater dose and threefold greater period in the present study) may explain, in part, the contradictory findings.

We further suggest that the difference in results from those of Rooney et al. (2002) was possibly due to differences in experimental model. Whilst Rooney et al. (2002) demonstrated in rats that insulin secretion increased along with the increase in the pancreatic creatine content, studies in humans do not support these findings. (Van Newman et al., 2003; Rooney et al., 2003; van Loon et al., 2004). Unlike charged guanidine compounds, such as arginine, creatine is not a potent insulin secretagogue. Although in vitro studies have indicated that creatine may enhance insulin secretion (Hill, 1928; Alsever et al., 1970; Marco et al., 1976), current studies have demonstrated that creatine supplementation does not increase insulin concentrations in humans (Green et al., 1996; Robinson et al., 1998; van Loon et al., 2004; Rooney et al., 2003;

Newman et al., 2003). Thus, differences between rats and humans in insulin metabolism could be another reason for the discrepancy in findings.

Despite the above discussion, however, we believe that the main variable responsible for the opposing results lies in the additive effect of exercise training. According to this, Eijnde et al. (2001b) have noted that ten weeks of rehabilitation training per se did not increase GLUT-4 above baseline level. However, the same training regimen in conjunction with oral creatine supplementation resulted in a marked increase of muscle GLUT-4 protein content. Likewise, the authors reported that muscle glycogen was significantly augmented only when exercise training was undertaken in conjunction with creatine supplementation. In the present study, both the CT and PT groups showed improvement in glucose tolerance as a consequence of exercise training (see Fig. 1), but the improvement in CT group was greater, indicating an additive effect of creatine supplementation.

We believe that our results are the first to demonstrate that long term creatine supplementation, combined with aerobic training at 70% of the $VO_{2max,}$ improves glucose tolerance in humans to a greater extent than aerobic training alone. In this we assume that training alone was effective in improving glucose tolerance. This is based on the significant change in AUC despite that we did not include a control group (no training, no treatment). The mechanisms responsible for the effect of creatine itself are not known unknown. It has been observed that creatine supplementation can augment GLUT-4 expression in rats (Ju et al., 2005) and GLUT-4 protein content in humans (Eijnde et al., 2001b). Muscle GLUT-4 is a primary determinant of insulin-stimulated muscle glucose uptake and metabolism (Pereira et al., 2005). Therefore, an improvement in insulin sensitivity and subsequent glucose tolerance would be expected. However, in accordance with others (Newman et al., 2003; van Loon et al., 2004) insulin sensitivity (i.e. HOMA and fasting insulin) were unaltered by creatine supplementation in the present study. Therefore, the improvement observed in glucose tolerance cannot be totally explained by alteration in insulin sensitivity. Accordingly, Eijnde et al. (2001a) showed that creatine-enhanced muscle glucose uptake (resulting in increased glycogen synthesis) was not due to an increase in circulating insulin levels or muscle insulin sensitivity. The authors speculated that other putative mechanisms may have been responsible including swelling of cells caused by increased intracellular osmolarity, creatine stimulation of other hormones (e.g. IGF-1 which has insulin-like effects), and/or decreased secretion of insulin-antagonistic hormones. Although the mechanism may not be known the evident improvement in glucose tolerance without hyperinsulinemia, brought about by long-term creatine supplementation in conjuction with aerobic training, warrants further investigation in the prevention and/or treatment of diseases such as metabolic syndrome and diabetes.

In conclusion, creatine supplementation in combination with moderate aerobic training over three months improved glucose tolerance in healthy sedentary males but did not alter insulin sensitivity. Further research should be directed to investigating the use of this in the treatment of diabetes, as well as the mechanism responsible.

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Authors' address: Antonio Herbert Lancha Junior, Av. Professor Mello Moraes, 65, Butantã 05508-900, São Paulo, SP Brazil,
E-mail: lanchajr@usp.br