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Effect of oral creatine supplementation in soccer players metabolism.

Efecto de la ingesta de un suplemento de creatina en el metabolismo de jugadores de fútbol.

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Abstract

The aim of the present study was to assess whether creatine can alter the metabolism of nitrogen compounds and performance in professional soccer players. The subjects were randomly divided into 2 groups: experimental (E; n = 17) and control (C; n = 14). Their initial evaluations included blood tests and nutritional intake. They then received a supplement consisting of 20 individual doses of creatine to be taken orally for 5 days, totaling 0.6 g.Kg-1 body weight per day (group E = 50% creatine + 50% dextrose; group C = 100% dextrose). On day 5, blood was collected from the resting subjects (PRE), and then 10 min (POST10) and 20 min (POST20) after they underwent an ergometric test. Nitrogen compounds and hematocrit were measured in each blood sample. There were no differences among the groups in the results of the physical examination, nutritional state, blood samples or performance. Serum ammonia levels measured after exercise were equal to those at rest. Serum urea increased in POST10 and POST20. In Group E, uremia was lower than in Group C in PRE, POST10 and POST20, indicating retention of protein and nucleotides.

Resumen

Este estudio objetiva determinar si la creatina puede alterar el metabolismo de los compuestos del nitrógeno y el desarrollo atlético en jugadores profesionales del fútbol. Los individuos fueron divididos aleatoriamente en 2 grupos: experimental (E; n = 17) y control (C; n = 14). Sus análisis de sangre incluidos evaluaciones iniciales y producto alimenticio. Entonces recibieron un suplemento que consistía en 20 dosis individuales de creatina que se tomará oral por 5 días, sumando 0.6 g.Kg-1.peso corpóreo por el día (grupo E = 50% creatina + 50% dextrosa; grupo C = 100% dextrosa). El el día 5, la sangre fue recogida a partir de los idividuos (PRE), y entonces de 10 minutos (POST10) y de 20 minutos (POST20) después de que experimentaran un test de esfuerzo máximo (GXT). Los compuestos del nitrógeno y el hematocrit fueron medidos en cada muestra de la sangre. No había diferencias entre los grupos en los resultados de la examinación física, del estado alimenticio, de las muestras de la sangre o del desarrollo atlético. Los niveles del amoníaco del suero midieron después de que el ejercicio fuera igual en descanso. La urea del suero aumentó de POST10 y de POST20. En el grupo E, la uremia era más baja que en el grupo C adentro PRE, POST10 y POST20, indicando la retención de la proteína y de los nucleotides.

Key words:ammonia, urea, creatine, soccer.

Palabras clave: amoníaco, uremia, creatina, fútbol.

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Introduction

Soccer is a sport that involves wide variations in intensity. During a single game, the emphasis on each energy system alternates; consequently, attaining the ideal balance of training is difficult and depends on knowledge of the metabolism of individual athletes (Stølen et al., 2005). A rest period at the end of a season is routine in the professional sport, and therefore a pre-season readjustment period is necessary when training is resumed. One concern during this period is that extreme proteolysis can cause overtraining. It is claimed that exercise strongly affects protein degradation, increasing uremia, and that this effect increases as athletes are less well-conditioned (Rennie and Tipton, 2000). About these questions, it is worthwhile to search for efficient ergogenic resources, in an attempt to increase the benefits of training (Ostojic and Mazic, 2002).

It is suggested that nitrogen metabolites participate in the resulting fatigue, because they are potential precursors of ammonia, which have been discussed as possible inducers of central and/or peripheral fatigue during exercise (Nybo and Secher, 2004). Studies have demonstrated that ammonia production in muscle can occur from the reactions of the purine nucleotide cycle (PNC)(Zhao et al., 2000). On the other hand, one cannot neglect the appearance of ammonia from deamination of some amino acids during physical activity (Mourtzakis and Graham, 2002). In addition to these factors, ammonemia is affected by enteric absorption of microbial products (Merrick and Edwards, 1995).

The genesis of ammonia via PNC during exercise is dependent on the rate of resynthesis of ATP and consequently of the phosphocreatine system (CrP). The high energy demand induced by exercise alters the ATP-ADP-AMP ratios, increasing the concentrations of ADP and AMP. Part of the AMP is deaminated by adenosine deaminase (ADA), with consequent production of IMP and ammonia (Zhao et al., 2000).

An increase in total muscle creatine (CrT) can exert an ergogenic effect in high-intensity exercise (Kreider, 2003) and in soccer players (Mujika et al., 2000; Ostojic, 2004). This effect can be explained by the increase of the rate of resynthesis of ATP during exercise and of CrP during recovery, delaying the appearance of fatigue. Because creatine supplementation increases the concentration of muscle CrP in many subjects, it is postulated that ADP rephosphorylation increases, reducing adenine degradation with consequent reduction of ammoniagenesis (Terjung et al., 2000).

The effect of creatine supplementation on ammonemia has been studied, but the results were inconclusive. Some studies showed no differences in serum ammonia concentrations between subjects taking supplements and the controls (Febbraio et al., 1985; Snow et al., 1998). Bellinger et al. (2000) observed that supplementation with creatine reduced ammonemia and uricemia during exercise, indicating probable conservation of nucleotides.

The effect of creatine supplementation may also be associated with protection against proteolysis. Previous studies have yielded conflicting results in relation to the changes in protein turnover with creatine supplementation. Two studies (Deldicque et al., 2005;

Havenetidis, 2005) showed that creatine can increase synthesis or reduce degradation of muscle protein during training. There are no specific studies on this type of variable in soccer players during pre-season training.

The aim of the present study was to measure the serum concentration of urea, ammonia, and uric acid during the first week of pre-season training and after intense exercise by professional soccer players taking a creatine supplement, and to assess the possible effect of creatine on their performance.

Material and method

The subjects were 31 professional soccer players who had approximately 30 days of rest. They were all healthy; between 21 and 31 years of age; used no drugs, dietary supplements, or anabolic steroids; participated voluntarily, and gave prior written informed consent. The experimental conditions were in accordance with the norms of the BRAZILIAN NATIONAL HEALTH COUNCIL, under RESOLUTION No. 196, promulgated on 10 October 1996, referring to scientific research on human subjects.

In a randomized double-blind, placebo-controlled design, the subjects were divided into 2 groups: experimental (E; n = 17) and control (C; n = 14). On the first day, all of them had physical examinations, received the supplements and were instructed in the experimental procedures. The athletes frequently carried out tests with Bruce's protocol in the same laboratory, and were therefore adapted to the equipment and the physical space.

An initial blood collection (BASE) served to determine the state of health of these athletes as well as the possibility of differences between the groups. Hematologic and serum chemical values evaluated were: erythrocytes; hemoglobin; hematocrit; M.C.V.; M.C.H.; M.C.H.C.; leucocytes; basophils; eusinophils; myelocytes; metamyelocytes; Bands; lymphocytes; atypical lymphocytes; monocytes; platelets; sodium; potassium; chlorides; serum iron; glucose; urea; creatinine; lipids; uric acid; globulin; albumin; and the albumin/globulin ratio.

Supplement was given as a loading dose, consisting of 20 individual doses to be consumed over 5 days (4 daily doses), totaling 0.6 $g.Kg^{-1}$ of body weight per day (group E = 50% creatine + 50% dextrose; group C = 100% dextrose). During this period all the subjects had daily sessions of conventional pre-competition soccer training.

During the 5 days when they were taking the supplement, the subjects kept logs of their food, which were later analyzed to quantify the macronutrients that they had taken in, and to calculate the percentages of protein, carbohydrates, and lipids (Table 1).

Table 1 - Characteristics of the subjects. Physical measurements and nutritional characteristics of the subjects.

Characteristics	E Group mean ± SD (Range)	C Group mean ± SD (Range)
Age (years)	25 ± 3 (21-30)	27 ± 1 (24-31)
Total Body Mass (Kg)	73,0 ± 1,8 (68,6-85,0)	73,9 ± 5,4 (65,1-98,0)
Carbohidrates (%)	54 ± 3 (38-68)	50 ± 6 (35-73)
Lipids (%)	29 ± 2 (18-38)	34 ± 5 (16-47)
Proteins (%)	17 ± 2 (8-24)	16 ± 1 (12-19)

There were no significant differences between the groups (mean ± SE, p>0.05).

On day 7, blood was collected from resting athletes (PRE), and they then underwent an ergometric test (GXT) according to Bruce's protocol. After the test, the athletes rested for 20 min, and during this period two new blood samples were taken, one at 10 (POST10) and another at 20 min (POST20). Ammonia, uric acid, urea and the hematocrit were measured in each sample. The tests were done between 14:00 and 17:00h, minimizing possible effects of the circadian rhythm. The experimental design is shown in Figure 1.

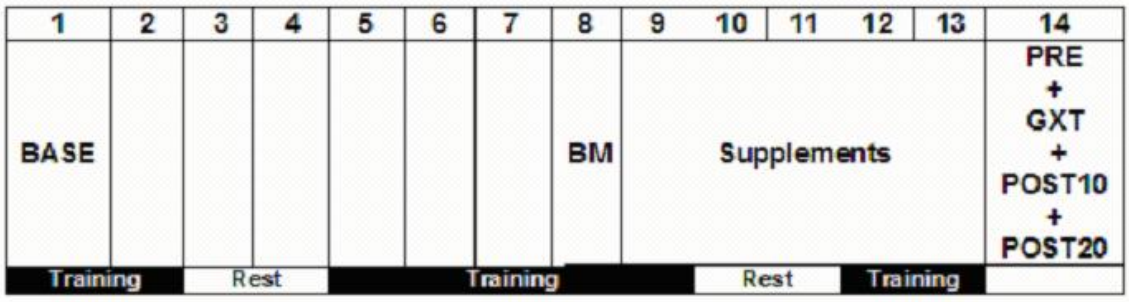

Figure 1 – Experimental design and timeline. On day 1, blood was sampled to assess hematological and biochemical parameters. On day 8, body measurements were taken and the subjects were instructed in taking the creatine supplement, and received a five-day supply. On day 14 all the subjects underwent an ergometric test, and their blood was sampled before and after the test. BASE = initial pre-training daily blood sampling; BM = body measurements; PRE = blood sampling prior to exercise; GXT = ergometric test; POST10 = blood sampling after 10 min; POST20 = blood sampling after 20 min.

The ergometric test was done on a Millenium™ treadmill (Imbramed, Brazil) in a climate-controlled room at 23.1 ± 0.5 ºC (mean ± SD). The serum dosages were done in the Bedalab laboratory (Campos dos Goytacazes, Rio de Janeiro, Brazil).

The results from the BASE and performance tests were analyzed using an unpaired Student's t test, to compare each of the variables between the groups. The level of significance adopted was 5% (= 0.05). For the data with repeated measures, a one-way ANOVA was used, and if necessary Tukey's post-hoc test, also with a 5% significance level. Statistical treatment was done using SPSS® 13.0 for Windows (LEAD Technologies, 2004).

Results

The physical measurements and nutritional profiles of the subjects were evaluated in order to assess possible differences between the groups, and distortions which might compromise the results of the study. Because food contains creatine, it was necessary to verify whether intake of macro-nutrients varied among the subjects. We found no differences between the two groups, or between subjects (Table 1).

A possible cause of erroneous interpretation of the results of metabolic studies is sample heterogeneity. To prevent metabolic alterations caused by changes in gas transport, by changes in nutrition, or the presence of infection or infestation, we evaluated the blood parameters and biochemical indicators of nutritional state of the subjects.

The hemograms of all the subjects were within the normal range for the population (Table 2). To assess the nutritional status of the athletes, we measured the concentrations of several bioavailable macro- and micronutrients. Serum protein levels indicated that dietary protein was adequate and well adjusted to consumption. Lipidograms indicated normal lipid metabolism within the parameters measured for most of the group, noting that all the individuals ate a standard breakfast (Table 3).

Table 2 – Hemogram of the subjects (mean ± SE) and population values**.** Before the beginning of the experiment, the cellular hematological and immunological status of all the subjects was evaluated.

	E Group mean ± SE (Range)	C Group mean ± SE (Range)	Popula-tional values
Erythrocytes x 10^6 (/mm^3)	5,2 ± 0,3 (4,6-5,4)	5,1 ± 0,9 (4,7-5,2)	5,4 ± 0,7
Hemoglobin (g/dl)	14,8 ± 0,2 (14,0-16,0)	15,0 ± 0,2 (13,9-16,2)	16,0 ± 2,0
Hematocrit (%)	44,8 ± 0,6 (40,7-48,6)	45,2 ± 0,7 (42,7-48,6)	47 ± 5
M. C. V. (μ^3)	88,6 ± 0,7 (83,5-91,1)	88,4 ± 0,8 (83,5-90,3)	87 ± 7
M. C. H. (ρgrams)	29,3 ± 0,3 (27,5-30,4)	29,2 ± 0,3 (27,5-30,3)	29 ± 2
M. C. H. C. (%)	33,2 ± 0,1 (33,0-33,5)	33,1 ± 0,1 (33,0-33,5)	35 ± 2
Leucocytes x 10^3 (/mm^3)	6,2 ± 0,3 (4,9-8,4)	6,1 ± 0,3 (4,9-8,4)	7,8 ± 3,0
Basophils (/mm^3)	39 ± 5 (0-67)	42,4 ± 5,6 (0-62)	0 a 200
Eusinophils (/mm^3)	198 ± 41 (79-641)	262 ± 62 (79-660)	0 a 700
Myelocytes (/mm^3)	0 (0-0)	0 (0-0)	0
Metamyelocytes (/mm^3)	0 (0-0)	0 (0-0)	0
Bands (/mm^3)	13 ± 13 (0-180)	16 ± 16 (0-211)	0 a 700
Segmented x 10^3 (/mm^3)	3,6 ± 0,2 (2,8-5,3)	3,4 ± 0,3 (1,6-5,4)	1,4 a 6,5
Lymphocytes x 10^3 (/mm^3)	1,7 ± 0,1 (1,4-2,4)	1,7 ± 0,1 (1,3-2,3)	1,2 a 3,4
Atypical Lympho. (/mm^3)	0 (0-0)	0 (0-0)	0
Monocytes (/mm^3)	502 ± 41 (180-673)	515 ± 46 (180-685)	100 a 600
Platelets x 10^3 (/mm^3)	251 ± 14 (177-326)	248 ± 17 (179-362)	150 a 450

There were no significant differences between the groups ($p>0.05$), and individually all fell within the normal range.

Table 3 – Mean values (± SE) for proteins, lipids, and serum glucose. The measurements were part of the evaluation of the nutritional status of the athletes before they began taking the supplement.

	E Group mean ± SE (range)	C Group mean ± SE (range)	Popula-tional Values
Total Proteins (%)	7,7 ± 0,2 (6,7-8,0)	7,6 ± 0,2 (6,7-8,0)	6,0 a 8,0
Albumin (%)	4,6 ± 0,1 (4,0-5,0)	4,4 ± 0,1 (4,0-4,9)	3,5 a 5,5
Globulin (%)	3,1 ± 0,2 (2,4-4,0)	3,1 ± 0,1 (2,4-3,9)	-
A/G	1,5 ± 0,1 (1,1-1,9)	1,4 ± 0,1 (1,1-1,8)	1,2 a 2,2
Total Lipids (mg/dL)	541 ± 19 (451-678)	539 ± 23 (455-678)	400 a 800
Glucose (mM)	5,5 ± 0,2 (4,0-5,8)	5,1 ± 0,2 (3,9-5,5)	3,6 a 6,1

(A/G) albumin/globulin ratio. There were no significant differences between the groups ($p>0.05$), and all values fell within the populational values.

Also, the most important blood-metal levels (Na^+, K^+, Cl^- e Fe^{++}) were within normal parameters (Table 4).

Table 4 – Measures of the electrolyte concentrations (mean ± SE) and populational values.

	E Group mean ± SE (range)	P Group mean ± SE (range)	Popula-tional Values
Na^+ (mEq/L)	139,5 ± 0,3 (137,0-141,0)	140,3 ± 0,4 (139,0-143,0)	132 a 144
K^+ (mEq/L)	4,2 ± 0,1 (4,0-4,6)	4,2 ± 0,0 (4,0-4,6)	3,6 a 5,0
Cl^- (mEq/L)	103,1 ± 0,4 (102,0-108,0)	102,8 ± 0,3 (102,0-104,0)	96 a 109
Fe^{++} (mcg/dL)	108,9 ± 11,2 (58,0-150,0)	105,1 ± 11,8 (58,0-150,0)	50 a 150

There were no significant differences ($p>0.05$) between the groups, and all values fell within the normal range.

Metabolic variation during exercise depends on the rates of production and removal of metabolites. To evaluate this capacity in our subjects, we measured several indicators of hepatic and renal functions. The serum concentrations of creatinine, urea, and uric acid were normal in the resting subjects, which shows that the main functions of hepatic and renal clearance were maintained (Table 5).

Table 5 – Mean (± SE) of the BASE concentration of nitrogen compounds. The serum parameters of these compounds were part of the hepatic and renal evaluation of the subjects, before they received the supplement.

	E Group mean ± SE (range)	P Group mean ± SE (range)	Populational Values
Urea (mM)	5,0 ± 0,5 (4,5-5,5)	4,7 ± 0,5 (4,0-5,3)	1,7 a 8,3
Creatinine (mM)	0,2 ± 0,1 (0,0-0,1)	0,2 ± 0,0 (0,1-0,2)	0,0 a 0,2
Uric Acid (mg/dL)	5,3 ± 0,4 (4,8-6,0)	5,7 ± 0,4 (4,9-6,6)	2,5 a 7,0

There were no significant differences ($p>0.05$) between the groups, and all the values fell within the normal range.

Hemodilution or hemoconcentration can affect the correct interpretation of the values obtained in the serum analysis; in certain kinds of exercise, volemia may vary (Gaebelein and Senay Jr, 1980). This variable was controlled through the hematocrit and hemoglobin concentration, which did not vary during the experimental protocol (data not shown). Therefore the other measurements could be made without the need to correct for volemia.

It has been suggested that ammonia may be involved in fatigue processes. To assess the variation of ammonia in our study, we measured ammonemia before and after exercise (10 and 20 min). The ammonemia levels measured before and after exercise did not differ between the groups at either sampling times ($p>0.05$) (data not shown).

Urea concentration increased about 60% in the control group, when we compare the PRE measurement with the findings at the BASE moment. This datum was not verified in supplemented group. After the exercise period, these concentrations varied in none of the groups, remaining elevated in group C (Figure 2).

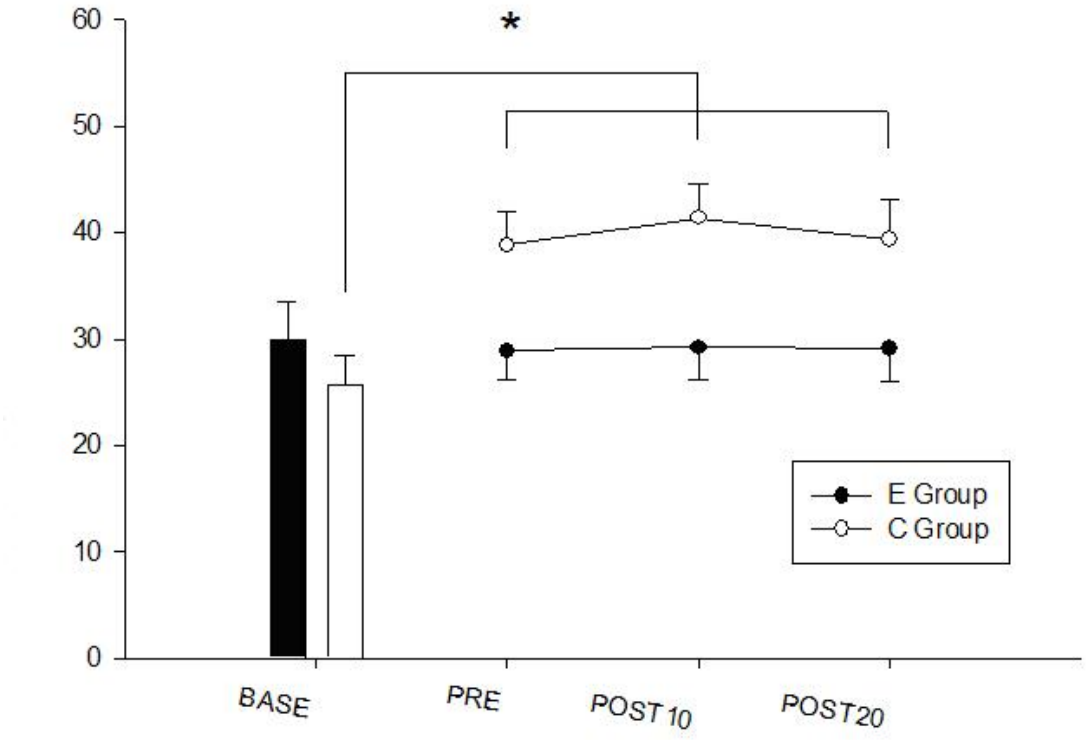

Figure 2 – Variation in urea concentration (mean ± SE). Uremia (mM) was measured prior to the beginning of the test and 10 and 20 min after the test, and was high in all measurements for group C after the period of supplementation, compared with the BASE measurements. The mean urea concentration in group C was higher than that in group E and in PRE and POST10 ($p<0.05$). * indicates increase in relation to the initial collection in group C ($p<0.05$).

Comparison of the uric acid concentrations before and after the exercise period showed equivalent variation in both groups, increasing about 20% between POST10 and PRE ($p<0.05$). Uricemia remained high, and at the same level at POST20 for both groups (Figure 3).

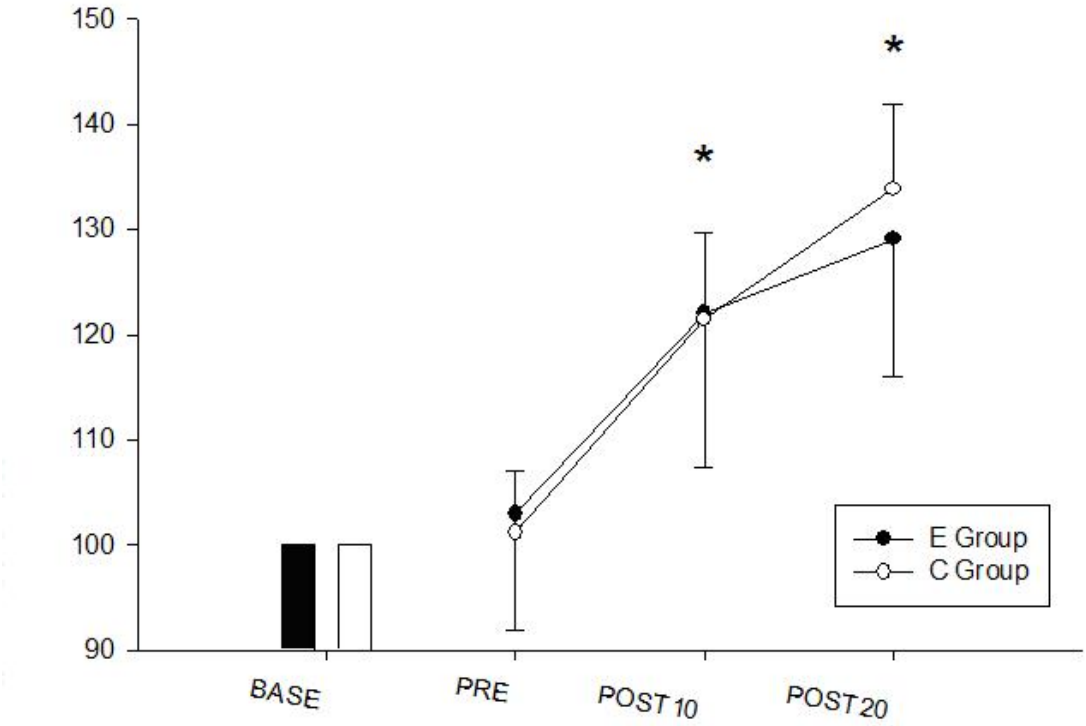

Figure 3 – Normalized variation in uric acid concentration (mean ± SE). Uric acid was measured before the beginning of the test and 10 and 20 min after the test. * indicates difference in relation to PRE in both groups ($p<0,05$).

Since the 1980s it has been known that creatine supplementation can exert a ergogenic effect during high-intensity exercise (Kreider, 2003). Our results for performance do not support this hypothesis, because we found no difference between the groups in the total time of execution of the GXT (Group E, 19 ± 1 min and Group C, 19 ± 1 min).

Discussion

The adequacy of Bruce's test for measuring aerobic endurance is debated because it can easily cause periferic fatigue in the legs and be interrupted before the VO_2max is reached. In this protocol, the treadmill inclination increases in each 3-minute stage, each time demanding more from the leg muscles, mainly in those individuals who do not routinely perform this type of movement (Kang et al., 2001).

Creatine supplementation is claimed to be an ergogenic resource for short-duration, high-intensity muscle performance. Therefore, differences between the groups might have been expected. The possible improvement in muscle performance might lessen the possibility of local fatigue, allowing the supplemented subject to stay longer on the treadmill than a subject who had not received the supplement. This hypothesis was not confirmed by our data, in which the athletes of both groups remained on the treadmill for equal periods. These data corroborate the findings of Biwer et al. (2003), who used an inclined ergometric treadmill and found no difference in the performance of the subjects taking the supplement.

Some studies have indicated greater efficiency of creatine supplementation in intermittent exercises (Mujika et al., 2000; Volek and Rawson, 2004), which was confirmed in women soccer players (Cox et al., 2002). The present study involved only a single gradual load test, and did not demonstrate any improvement in performance in supplemented subjects.

Resuming training after a vacation period induces high (but subclinical) uremia in soccer players; it is speculated that the training requirements for these athletes in relatively poor condition may cause more protein breakdown and consequent amino-acid oxidation, increasing urea production (Dohm et al., 1997; Van Loon et al., 1999). In this study, uremia of the non-supplemented subjects increased; however, in the subjects taking the creatine supplement, the mean urea concentration remained unchanged.

Our data corroborate those in the literature; i.e., the return to training leads to an increase in uremia. It is postulated that this change occurs from the increase in proteolysis and amino acid oxidation (Hartmann and Mester, 2000; Warburton et al., 2002; Petibois et al., 2003). Extreme protein breakdown can cause an overtraining syndrome, increasing the possibility of injuries and leading to a decline in performance (Hartmann and Mester, 2000). We might explain this finding assuming that reduction of nucleotide degradation during training can lessen the anaplerotic need for amino acids, thus reducing urea production. Bicyclists showed a reduction in nucleotide breakdown during and after 1 h of exercise in individuals taking a creatine supplement: the metabolites generated by the breakdown of traditional nucleotide fatigue markers, which would make possible better performance in long-duration exercises (Bellinger et al., 2000).

We can to correlate maintenance of uremia with endogenous creatine synthesis. Creatine synthesis shares a stage with the urea cycle, the generation of ganidinoacetate from glycine and arginine bonding (Wyss and Kaddurah-Daouk, 2000). It has been previously demonstrated that this reaction is inhibited at increased creatine concentrations, such as those generated during the period of supplementation. It is still not known whether this decrease affects the urea cycle, but the data obtained in this study suggest that urea synthesis may itself decline (Wyss and Kaddurah-Daouk, 2000). According to published findings, a third postulate is that creatine supplementation induces an increase in muscle protein synthesis (Deldicque et al., 2005). The increase in protein synthesis reduces nitrogen excretion in the form of urea. This metabolic change may have contributed to the lower uremia in the athletes taking this supplement.

The results showed that the subjects taking creatine had less uremia than the control group. In patients with hepatic disease, the reduction of uremia can be followed by an increase in ammonemia, leading to problems such as hepatic encephalopathy (Butterworth, 2002). For athletes, it is postulated that increases in sub-clinical ammonemia may lead to poorer performance (Nybo and Secher, 2004; Nybo et al., 2005). Our results did not show increases in ammonemia induced by the creatine supplementation; indeed, urea concentration was lower in the athletes taking creatine.

Because these athletes were returning from a period of inactivity, we expected that the post-exercise ammonia concentration would rise. The ammonemia measured in this study was not different between the groups or the sampling times, the time post-exercise

(long) or the requirements (low) of Bruce's test for the athletes may be the indicators for the values obtained. In passive rest after exercise, ammonia concentrations return to normal after only 5 to 7 min (Hellsten et al., 1999; Ogino et al., 2000).

Increases in ammonemia are induced by nucleotide breakdown, and are followed by increases in uric acid concentration. The data obtained from the measurement of uric acid allow us to postulate that ammonemia may have increased during the exercise period. However, the 10-min interval between the end of the exercise and the first blood sample was long enough so that the ammonia produced was purified. We observed increases in uricemia 10 and 20 min after the exercise period ended. The data from this study corroborate those found in the literature, which show that ammonia concentration is high at the beginning of the rest period, and uric acid is elevated after 10 min of rest (Hellsten et al., 1999).

Conclusion

The main findings of this study are that a creatine supplement can affect urea synthesis, and can indirectly affect amino acid metabolism during training; without, however, affecting performance in gradually intensifying exercise.

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