Creatine Supplementation Associated with Resistance Training Does Not Alter Renal and Hepatic Functions

EXERCISE AND SPORTS SCIENCES

ORIGINAL ARTICLE

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ABSTRACT

Creatine is the most popular nutritional supplement widely used to improve performance in activities that involve exercise of short duration and high intensity. However, the complications arising from its use are not fully elucidated. The aim of this study was to evaluate the effects of two doses of creatine supplementation on renal and hepatic function in healthy adults during eight weeks of resistance exercise training. Biochemical tests were performed on 35 athletes randomly distributed into three groups, placebo (PLA, n = 12), creatine (CRE1, n = 12) and creatine2 (CRE2, n = 11) before and after eight weeks of resistance training. In a double-blind design, the volunteers were supplemented (20 g/day) with creatine (CRE1, CRE2) or placebo (PLA) for seven days and at the 53 subsequent days with 0.03g/kg of body weight of each supplement (CRE1, PLA) and 5g/day for CRE2. There was no intervention in the composition of their diets, which were recorded and analyzed. The results of biochemical tests conducted remained within normal ranges. Creatinine values increased by 12.2% for CRE1 and 9.0% for CRE2, whereas decreased by 4.7% in PLA; however, these values did not exceed normal rates. The values of liver function tests declined in nearly all fractions in all treatments, not being statistically significant, though. It is concluded that creatine supplementation at the dosages used (0.03g/kg and 5g/day) for healthy subjects during eight weeks does not alter hepatic or renal function, hence under the conditions of this study, creatine was considered safe.

Keywords: creatine, biochemical tests, nutritional supplementation, adverse effects.

INTRODUCTION

Creatine supplementation has become popular from the Olympic Games of Barcelona in 1992 and is currently one of the most popular protein supplements used by athletes and physical activity practitioners[1,2].

There is evidence that the creatine amount stored may be the limiting factor of physical performance in high intensity and short duration exercises. Thus, the increase of its storage through supplementation becomes a strategy to increase its offer and, consequently, to boost the resynthesis of adenosine triphosphate (ATP) in up to 30%[3].

Shao and Hathcock[4], after extensive work, verified that after two and a half decades of experimental and clinical studies with different dosage and times of supplementation, in only two cases of volunteers supplemented with creatine renal complication have been reported, but which came from periods previous to these experiments. However, despite the strong evidence of this substance as an ergogenic agent, it is still not unkown about possible hepatic and renal alterations derived from creatine supplementation, demanding hence further studies on this supplementation safety[2,5,6].

A hypothesis that creatine supplementation modifies the renal and hepatic functions in individuals clinically normal is brought about from the shortage of evidence on the potential adverse effects derived from the supplementation with monohydrate creatine in the hepatic and renal function. Thus, the aim of this research was to evaluate the effects of two doses of creatine supplementation in the renal and hepatic functions of healthy adults during eight weeks of bodybuilding training (resistance exercises).

METHODS

35 male individuals, aged between 18 and 42 years, with a minimum of two consecutive months of training with resistance exercises (bodybuilding) were selected to participate in this study. All volunteers presented minimum training regularity of four times per week, answered to the anamnesis constituted of personal and nutritional clinical history, and did not make use of any kind of food supplement in the last six months, besides being clinically healthy, normal and non-smokers. The research was approved by the Ethics in Human Research Committee of the College of Health Sciences of the University of Brasília (# 083/2006).

The volunteers were submitted to anthropometric measurements of body weight and height as well as blood biochemical exams, uranalysis and were randomly divided in three groups. The experimental groups (CRE1, n = 12) and (CRE2, n = 11) were submitted to monohydrate creatine supplementation (MIDWAY INTERNATIONAL LABS, Goiás) while the control group (PLA, n = 12) received placebo, maltodextrin (MIDWAY). The supplements were stored in plastic wrap with similar color and texture, which did not allow that the used supplement could be identified. Supplements weighting and distribution were under the responsibility of a laboratory technician, which guaranteed the double-blind character of the study.

Purity, physical-chemical and microbiological analyses of the monohydrate creatine were performed by three independent labo-

ratories. The laboratories performed the identification by infra-red and odor aspect and loss determination by desiccation. The results confirmed 99.9% of purity. The physical-chemical analysis of the sample presented a crystalline, white and odorless powder with humidity content ranging between 3.9-10% in agreement with the reference values. The microbiological analysis reported absence of coliforms, salmonella, aureus, bacillus and the counting of mesophyll were of 40 u.f.c/g in accordance with the specification – less than 1.000 u.f.c/g.

Supplementation was administered in two moments. On the first, during a period of seven days, the CRE1, CRE2 and PLA groups ingested 20g of the respective supplements, distributed in four equal doses during the day (breakfast, lunch, snack and dinner). The second moment occurred on the following seven weeks, with ingestion in single dose administered one hour after the training. The control (PLA) and CRE1 groups ingested 0.03g/kg of total body weight of maltodextrin and creatine, respectively, and 5g of creatine were ingested by the CRE2 group. On both moments, the creatine was ingested dissolved in about 250ml of carbohydrate drink and the chosen quantities (doses) are justified for being the mostly used (which allows future comparisons) or the mentioned on the manufacturer's label (5g).

The exams for hepatic and renal function evaluation were performed in the Clinics Hospital of the Federal University of Goiás and were constituted of complete hemogram, urea, creatinine, proteinogram, lipid profile, total bilirubin, direct and indirect, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALKP), protrombine time (PT) and simple urine exam (EAS-Sedimentoscopy Abnormal Elements).

In order to control diet, the volunteers were submitted to the following instruments: eating inquiry and daily eating record. The 24-hour eating record consisted of reporting the food eaten on the day previous to the interview, and the food ingestion was estimated through the daily record by the self volunteer. In both cases, the data were collected in two non-consecutive days, according to guidelines from the Institute of Medicine, which allowed estimating the food and the respective portions ingested by the participants for determination of the daily energetic cost and macronutrients after processing in the NUTWIN program®.

As inclusion criteria, the three groups were submitted to the resistance exercise training program performed in three health clubs of the city of Goiânia, with supervision of physical education professionals. The training frequency control was performed daily and the training periodicity was of four times per week with approximate duration of one hour and 30 minutes. The training was composed of three sets of eight to 12 repetitions, with rest interval of one minute. The programs were differentiated in A, B and C during the week and the muscular groups were predominately divided in the following manner: training A – chest and triceps exercises; training B – back and biceps exercises; and training C – shoulder and leg exercises. Abdominal exercises were performed in all trainings. Aerobic part was subsequently on bicycle or treadmill for 10 to 20 min.

In order to verify the effects of the experiment on the hepatic and renal functions, the volunteers were submitted to the evaluations (biochemical and nutritional exams) before (PRE) the first moment and after the second moment (POST), that is, after eight weeks of supplementation and training.

In order to analyse the Pre and Post conditions of the dependent variables (nutritional evaluation and biochemical analysis), Student's t test for paired samples was applied. Multiple comparisons using Bonferroni correction (post hoc) were used when significant differences were found between the means of the groups (by treatment) compared with ANOVA (one way). Analysis of covariance (ANCOVA) with initial results (PRE) of each variable as covariant was used for analysis of differences between procedures (treatments) with and without supplementation between groups, since differences between the initial results (PRE) of the groups were found. The significance level used was $p < 0.05$. The data statistical treatment was performed through the computer package SPSS (Statistical Package for Social Science for Windows) (version 13.0 – 2005).

RESULTS AND DISCUSSION

The anthropometric characteristics are described in table 1 and it can be verified that the groups are similar and belong to the same population ($p < 0.05$). Since the initial results (PRE) obtained between groups were significantly different, during the comparison between groups multivariate analysis (ANCOVA) with initial results (PRE) as covariants was the choice for the comparison between groups (treatments).

The total and of macronutrients energetic values did not differ ($p < 0.05$) between the Pre and Post values for groups PLA, CRE1 and CRE2, (table 2) and did not present significant alterations when compared by treatment (supplementations). Similar results were found by Kilduff et al.[7], Machado et al.[8] and Arciero et al.[9].

Table 1. Characteristics of the volunteers per treatment group.

Groups	n	Age (years)	BM (kg)	Height (cm)	BMI (kg.m-2)
PLA	12	23.0 ± 3.2	69.4 ± 8.3	175.0 ± 7.1	22.4 ± 2.3
CRE1	12	24.3 ± 4.9	71.9 ± 9.1	173.8 ± 7.9	23.7 ± 2.6
CRE2	11	25.2 ± 7.4	66.9 ± 7.8	174.1 ± 3.4	22.0 ± 2.2

PLA: placebo group CRE1: creatine 0.03g/kg/Day group; CRE2: creatine 5g/Day group. Values: mean ± standard deviation; BM: body mass; BMI: body mass index.

Table 2. Total energetic and macronutrient values per treatment group.

Measurements	Groups	Pre		Post		p
Total Energetic Value (kcal)	PLA	2.833.7 ±	556.7	2.831.6 ±	550.1	0.6342
	CRE1	2.991.8 ±	623.4	2.990.8 ±	622.9	0.7759
	CRE2	3.310.9 ±	410.0	3.296.5 ±	409.1	0.2352
Carbohydrate (g)	PLA	380.3 ±	95.5	384.2 ±	97.0	0.1842
	CRE1	429.7 ±	102.6	423.4 ±	104.7	0.0505
	CRE2	464.3 ±	78.5	466.8 ±	74.1	0.4265
Protein (g)	PLA	130.2 ±	28.8	130.2 ±	28.3	0.9874
	CRE1	126.6 ±	31.7	126.8 ±	31.4	0.7376
	CRE2	144.7 ±	19.8	146.7 ±	17.9	0.0742
Lipids (g)	PLA	89.1 ±	19.6	87.6 ±	18.2	0.2320
	CRE1	87.7 ±	15.8	90.1 ±	17.7	0.1344
	CRE2	97.2 ±	8.0	95.2 ±	10.4	0.3595

Values: mean ± standard deviation; Pre: before training; Post: after training; p: significance level; PLA: placebo group CRE1: creatine 0.03g/kg/day group; CRE2: creatine 5g/day group.

Concerning the indicators of renal activity (table 3), significant difference has been observed ($p < 0.05$) in the Pre and Post creatinine values (intra-group) for all groups. There was percentage decrease of 4.7% for group PLA, while in the CRE1 and CRE2 groups increase (12.2 and 9.0%, respectively) has occurred after the supplementation period; nonetheless, these values did not surpass the normality indices, being considered with no clinical relevance. The total proteins decreased between the Pre and Post values in group CRE1 ($p < 0.05$), representing decrease of 4.6% of the protein profile. The PLA, CRE1 and CRE2 groups did not significantly differ concerning the albumin and globulin fraction values when compared the Pre and Post values were compared. Urea content (dosed in the serum) decreased from the Pre to the Post moments only in the CRE2 group (–8.9%). Robinson et al.[10] observed similar results to these concerning urea. Machado et al.[8] found increase of 60% in urea in the control group, and the group supplemented with creatine kept its values similar to the ones previous to supplementation, demonstrating hence low interference of creatine in this exam.

Table 3. Indicators of renal activity in the different treatments.

Measurements	Groups	Pre		Post		p	Reference values	
							Minimum	Maximum
Creatinine - Dosing in the serum (mg/dL)	PLA	1.1 ±	0.1	1.0 ±	0.1	0.0261	0.7	1.3
	CRE1	1.0 ±	0.1	1.2 ±	0.2	0.0172		
	CRE2	1.0 ±	0.1	1.1 ±	0.1	0.0096		
Total proteins proteinogram (g/dL)	PLA	7.1 ±	0.5	6.9 ±	0.2	0.1307	6.0	8.0
	CRE1	7.3 ±	0.4	7.0 ±	0.4	0.0406		
	CRE2	7.0 ±	0.3	7.0 ±	0.4	0.8461		
Albumin - proteinogram (g/dL)	PLA	4.6 ±	0.2	4.6 ±	0.2	0.7609	3.5	5.5
	CRE1	4.6 ±	0.3	4.5 ±	0.2	0.4822		
	CRE2	4.4 ±	0.2	4.6 ±	0.4	0.2622		
Globulin - proteinogram (g/dL)	PLA	2.6 ±	0.4	2.3 ±	0.3	0.0996	1.5	3.5
	CRE1	2.7 ±	0.4	2.4 ±	0.3	0.0848		
	CRE2	2.5 ±	0.4	2.4 ±	0.6	0.3188		
Urea – dosing in the serum (G/dL)	PLA	31.9 ±	7.7	31.3 ±	7.6	0.7603	10.0	50.0
	CRE1	32.0 ±	8.4	28.4 ±	7.1	0.1195		
	CRE2	34.6 ±	3.1	31.5 ±	5.8	0.0223		

Values: mean ± standard deviation; PRE: before training; POST: after training; p: significance level; PLA: placebo group; CRE1: creatine 0.03g/kg/day group; CRE2: creatine 5g/day group; Reference values: male adults.

It is worth mentioning that none values of the indicators of renal activity surpassed the normality indices; however, when compared with the placebo, significant difference was observed in the creatinine values between the groups supplemented with creatine in the two doses (PLA-CRE1, $p = 0.0013$ and PLA-CRE2, $p = 0.00136$). Such fact certainly indicates the creatine depuration due to the higher offer obtained through supplementation. These results are in agreement with the literature, since the creatine dosing variability administered in supplementation was of 10 to 20g/day during four years[4,10,11]. Supplementation for over seven days promotes cumulative effect in the body, reflecting for about 30 days after its end[12]. Robinson et al.[10] have referred that after this period there is a tendency of decrease in serum creatinine for the values previous to supplementation.

The hemogram results did not present significant difference (table 4) between the Pre and Post-treatment analyses, except for the hematocrit which increased 4% in the CRE2 group ($p < 0.05$), which can represent hematologic response to the systematized training. Milasius et al.[13] when analysed the effect of creatine supplementation with associated multivitamin complex observed a tendency of increase of hemoglobin rates in the supplemented group. Robinson et al.[10] and Machado et al.[8] did not observe significant increase in the hematocrit and hemoglobin between the creatine pre and post-supplementation.

Table 4. Hematological indicators.

Measurements	Groups	Pre		Post		p	Reference values	
							Minimum	Maximum
Hemoglobin – hemogram (g/dL)	PLA	15.5 ±	0.9	15.5 ±	0.9	0.9402	14.0	18.0
	CRE1	15.2 ±	1.0	15.0 ±	1.0	0.4234		
	CRE2	15.0 ±	0.9	15.0 ±	1.0	0.7834		
Hematocrit – hemogram (%)	PLA	45.7 ±	2.3	46.4 ±	2.7	0.4077	41.0	50.0
	CRE1	45.3 ±	3.3	44.9 ±	2.6	0.4108		
	CRE2	43.4 ±	2.1	45.1 ±	3.0	0.0414		

Values: mean ± standard deviation; Pre: before training; Post: post-training; p: significance level; PLA: placebo group; CRE1: creatine 0.03g/kg/day group; CRE2: creatine 5g/day group; reference values: male adults.

Concerning the hepatic functioning (table 5), the results of the exams did not present intra-group differences (Pre x Post). The aspartate aminotransferase (AST) values increased ($p < 0.042$) in the CRE2 group in the post-treatment when compared with the PLA group, but with no important clinical significance. Almada et al.[14] did not observe alterations in the levels of serum enzymes levels used to evaluate the hepatic function during eight weeks of supplementation. The data of the present study are in agreement with the studies by Earnest et al.[15], which did not find significant alterations of the bilirubin fractions when supplementation occurred with 20g/day for five days and 10g on the 51 remaining days. None responses different from the already existing in the literature about the hepatic function was found[5,10,15-17].

The lipid profile (table 6) did not suffer significant alterations when the Pre and Post results were compared; however, when the groups were compared, significant improvement in the total cholesterol values was observed for the CRE2 group ($p = 0.0398$). Creatrine seems to play a positive effect in the lipid profile[9,18] concerning the reduction in the total cholesterol, factions and triglycerides values, but none explanation on the possible mechanism involved in this alteration was found.

Regarding the simple urine exam, only the leucocytes presented alterations between the Pre and Post eight weeks of supplementation (table 7); however, there was no indication of abnormality and the levels were kept below the maximum reference value. Moreover, proteins, glucose, ketones, billiary pigments and hemoglobin were absent in the urine.

Table 5. Indicators of hepatic activity in the different treatments.

Measurements	Groups	Pre		Post		p	Reference values	
							Minimum	Maximum
Total bilirubin – dosing in the serum (mg/dL)	PLA	1.2 ±	0.4	1.0 ±	0.3	0.1231	0.3	1.1
	CRE1	1.2 ±	0.6	1.2 ±	0.5	0.8074		
	CRE2	1.0 ±	0.4	1.0 ±	0.3	0.8395		
Direct bilirubin – dosing in the serum (mg/dL)	PLA	0.1 ±	0.0	0.1 ±	0.0	0.3121	0.1	0.4
	CRE1	0.1 ±	0.1	0.1 ±	0.0	0.4991		
	CRE2	0.1 ±	0.0	0.2 ±	0.3	0.3134		
Indirect bilirubin – dosing in the serum (mg/dL)	PLA	1.0 ±	0.3	0.9 ±	0.3	0.0795	0.3	0.8
	CRE1	1.1 ±	0.6	1.1 ±	0.5	0.8695		
	CRE2	0.9 ±	0.4	0.9 ±	0.3	0.7200		
Aspartate aminotransferase (UI/L) - AST	PLA	24.9 ±	5.6	22.2 ±	7.9	0.1756	10.0	35.0
	CRE1	22.8 ±	8.2	22.3 ±	7.9	0.8433		
	CRE2	21.8 ±	4.5	24.3 ±	6.7	0.3442		
Alanine aminotransferase (UI/L) - ALT	PLA	19.9 ±	8.3	17.5 ±	6.5	0.3152	10.0	40.0
	CRE1	24.1 ±	9.2	21.0 ±	5.6	0.3069		
	CRE2	24.4 ±	6.9	25.1 ±	10.0	0.8905		
Prothrombin activity – prothrombin time (%)	PLA	74.1 ±	11.2	75.4 ±	8.0	0.5407	70.0	100.0
	CRE1	75.4 ±	7.8	77.2 ±	9.1	0.4118		
	CRE2	82.7 ±	3.7	80.3 ±	5.9	0.2930		
Alkaline phosphatase (U/L)	PLA	184.6 ±	50.1	171.3 ±	45.3	0.1713	80.0	300.0
	CRE1	178.7 ±	63.5	165.0 ±	39.2	0.2180		
	CRE2	165.8 ±	52.0	163.5 ±	40.4	0.8225		

Values: mean ± standard deviation; Pre: before training; Post: post-training; p: significance level; PLA: placebo group; CRE1: creatine 0.03g/kg/day group; CRE2: creatine 5g/day group; Reference values: male adults.

Table 6. Lipid profile.

Measurements	Groups	Pre		Post		p	Reference values	
							Minimum	Maximum
Total cholesterol (mg/dL)	PLA	141.3 ±	27.8	144.2 ±	28.6	0.4457	-	200.0
	CRE1	147.1 ±	24.4	152.8 ±	24.9	0.1950		
	CRE2	141.6 ±	30.6	136.5 ±	32.0	0.1157		
HDL cholesterol (mg/dL)	PLA	36.3 ±	8.9	37.1 ±	5.3	0.6761	45.0	-
	CRE1	42.7 ±	7.2	42.5 ±	10.7	0.9318		
	CRE2	35.8 ±	9.7	34.5 ±	7.8	0.3485		
LDL cholesterol (mg/dL)	PLA	91.6 ±	20.2	93.4 ±	23.9	0.5682	-	130.0
	CRE1	85.5 ±	21.9	88.2 ±	17.7	0.5628		
	CRE2	89.7 ±	23.6	84.5 ±	27.7	0.1524		
VLDL cholesterol (mg/dL)	PLA	13.9 ±	4.0	14.2 ±	6.6	0.8292	-	40.0
	CRE1	19.4 ±	11.9	22.6 ±	11.9	0.1327		
	CRE2	16.4 ±	3.6	18.0 ±	4.9	0.2912		
Triglycerides (mg/dL)	PLA	69.5 ±	19.8	70.9 ±	32.8	0.8292	-	150.0
	CRE1	97.1 ±	59.6	113.2 ±	59.7	0.1327		
	CRE2	82.1 ±	18.2	89.9 ±	24.3	0.2912		

Values: mean ± standard deviation; PRE: before training; POST: post-training; p: significance level; PLA: placebo group; CRE1: creatine 0.03g/kg/day group; CRE2: creatine 5g/day group; reference values: male adults. HDL: high-density lipoprotein; LDL: low-density lipoprotein; VLDL: very low-density lipoprotein.

Table 7. Main indicators of the urine simple exam – EAS.

Measurements	Groups	Pre		Post		p	Reference values	
							Minimum	Maximum
Leukocytes in urine (per ml)	PLA	3145.8 ±	2803.1	3583.3 ±	3492.4	0.7425	-	10.000
	CRE1	2875.0 ±	2912.6	5012.5 ±	3518.4	0.0553		
	CRE2	5772.7 ±	3640.8	3454.5 ±	2114.9	0.0452		

Values: mean ± standard deviation; PRE: before training; POST: post-training; p: significance level; PLA: placebo group; CRE1: creatine 0.03g/kg/day group; CRE2: creatine 5g/day; group. Reference values: male adults.

Pritchard and Kalra[19] report a case of kidney failure after creatine supplementation; however, the patient already presented kidney disease previous to the supplementation. Robinson[20] reported a case of rhabdomyolysis (disorder which involves kidney injury caused by toxic effects of the muscle cells content) and acute kidney failure and highlighted the use of maintenance doses five times higher than the recommendation, which could have predispose the patient to this pathology and concluded that further studies on creatine safety with higher doses and for more prolonged periods are necessary. Barisic et al.[21] concluded that patients with previous renal diseases should avoid creatine supplementation. Yoshizumi and Tsourounis[22] revised 12 papers and concluded that individuals with kidney disease history or those who take nephrotoxic medication associated with creatine increase the risk of kidney disorder. Supplementation can increase the creatinine levels, which contribute as a false indicator of kidney disorder.

Thorsteinsdottir et al.[23] reported that a 24-year old subject presented acute kidney failure after consumption of varied supplements (including creatine) associated with intense bodybuilding training and it was reverted after the supplements suppression. In this case, there was not control of ingestion of food, water and supplements, neither of previous biochemical exams, factors which certainly argue on the statement that creatine supplementation is the exclusive cause of this acute kidney failure. The reported cases of undesirable effects with creatine supplementation were independently studied and relevant facts such as: pre-existing kidney diseases, overdose, prolonged supplementation and use of simultaneous supplements should be stressed considering the lack of control of the intervenient variable. This situation makes it impossible to conclude whether creatine supplementation is responsible for kidney complications.

Acute or chronic creatine supplementation (10 weeks) did not increase renal stress in healthy individuals, as evaluated by many serum and urinary markers[12,15,16]. Likewise, adverse effects of creatine supplementation with low doses (1.5g) for prolonged periods (one to five years) on the renal function have not been reported either. Review studies[24-25] which analysed the short and long run renal and hepatic function with creatine supplementation did not find any alteration in the results of the same biochemical exams analysed in our study.

Moreover, when the renal function[16,26,27] and hepatic function[17,20,28], both in the short run with high doses and long run with low doses of creatine supplementation, did not observe any dysfunction. Bemben and Lammont[29] did not report any adverse effect in bibliographic review on the effects of creatine

supplementation in many organs. The International Society of Sports Nutrition[30] concluded that creatine is safe, legal and efficient. Shao and Hathcock[4] evaluated the risk of creatine use in studies of medium (28 days) and long run (until one year), in which creatine supplementation followed in its great majority the 20 grams dose on the first week and 5g/day on the following ones. No adverse effect has been observed in studies involving healthy individuals as well as patients, proposing hence that the maintenance dose of 5g/day seems to be safe.

It was concluded that creatine supplementation in the used doses (0.03g/kg and 5g/day) associated with resistance training does not alter hepatic or renal functions in the studied sample. The 0.03g/kg dose of body mass per day (2 to 3g of creatine per day) demonstrated results similar to the ones in the 5g dose in the eight weeks, corroborating the results found in the reviewed literature. Finally, it was observed that the use of creatine supplementation for healthy individuals for eight weeks, when following the protocols, is safe.

All authors have declared there is not any potential conflict of interests concerning this article.

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