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Long-term creatine supplementation does not significantly affect clinical markers of health in athletes

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Abstract

Creatine has been reported to be an effective ergogenic aid for athletes. However, concerns have been raised regarding the long-term safety of creatine supplementation. This study examined the effects of long-term creatine supplementation on a 69-item panel of serum, whole blood, and urinary markers of clinical health status in athletes. Over a 21-month period, 98 Division IA college football players were administered in an open label manner creatine or non-creatine containing supplements following training sessions. Subjects who ingested creatine were administered 15.75 g/day of creatine monohydrate for 5 days and an average of 5 g/day thereafter in 5–10 g/day doses. Fasting blood and 24-h urine samples were collected at 0, 1, 1.5, 4, 6, 10, 12, 17, and 21 months of training. A comprehensive quantitative clinical chemistry panel was determined on serum and whole blood samples (metabolic markers, muscle and liver enzymes, electrolytes, lipid profiles, hematological markers, and lymphocytes). In addition, urine samples were quantitatively and qualitative analyzed to assess clinical status and renal function. At the end of the study, subjects were categorized into groups that did not take creatine (n = 44) and subjects who took creatine for 0–6 months (mean 4.4 ± 1.8 months, n = 12), 7–12 months (mean 9.3 ± 2.0 months, n = 25), and 12–21 months (mean 19.3 ± 2.4 months, n = 17). Baseline and the subjects' final blood and urine samples were analyzed by MANOVA and 2 × 2 repeated measures ANOVA univariate tests. MANOVA revealed no significant differences ($p = 0.51$) among groups in the 54-item panel of quantitative blood and urine markers assessed. Univariate analysis revealed no clinically significant interactions among groups in markers of clinical status. In addition, no apparent differences were observed among groups in the 15-item panel of qualitative urine markers. Results indicate that long-term creatine supplementation (up to 21-months) does not appear to adversely effect markers of health status in athletes undergoing intense training in comparison to athletes who do not take creatine. (Mol Cell Biochem **244**: 95–104, 2003)

Key words: ergogenic aids, nutrition, safety, exercise, renal function, muscle, metabolism

Introduction

Creatine is a naturally occurring amino acid that is obtained from the diet and/or synthesized endogenously from the amino acids glycine, arginine, and methionine [1, 2]. Approximately 95% of creatine is stored in skeletal muscle while the remaining 5% is stored the heart, brain, and testes [3]. Of this, approximately two thirds of creatine is stored as phos-

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phocreatine with the remaining creatine comprising the free creatine pool [4]. Creatine supplementation (e.g. 20 g/day × 5 days) has been consistently reported to increase muscle creatine and phosphocreatine typically by 15–40% [4–6]. Theoretically, increasing the availability of phosphocreatine would enhance cellular bioenergetics of the phosphagen system [1, 2, 5–7] as well as the shuttling of high-energy phosphates between the mitochondria and cytosol via the creatine phosphate shuttle [8–10].

In support of this contention, approximately 70% of studies that have evaluated the potential ergogenic value of creatine supplementation have reported significant improvements in performance particularly those involving high-intensity exercise and/or training [2, 3, 7]. There is also recent evidence that creatine supplementation may provide therapeutic benefit for patients with a variety of metabolic disorders [11–15], neuromuscular diseases [16–21], as well hasten recovery following immobilization [22]. These findings have indicated that creatine may serve as a promising ergogenic aid for athletes as well as may offer some clinical benefit for certain populations.

The only side effect that has been consistently reported has been weight gain which may be a desired effect for many athletes and patient populations [1–3, 7, 23]. Despite this apparent safety record, concerns have been raised in the popular media and scientific community regarding the safety of creatine supplementation [23–28]. In this regard, concerns have been raised that creatine supplementation may promote long-term suppression of creatine synthesis, increase renal stress, promote muscle and liver damage, alter fluid and electrolyte status, and/or cause unknown long-term side effects [26, 27]. In addition, creatine has been anecdotally suggested to increase gastrointestinal upset, cause diarrhea, promote cramping and dehydration, and increase the incidence of musculoskeletal injury [2, 23, 27].

Recent studies have attempted to determine the validity of these anecdotally reported concerns. For example, a number of studies have evaluated the effects of short-term creatine supplementation (e.g. 5 days–12 weeks) on thermal stress/dehydration [29–33], cramping [31, 34–43], electrolyte status [31, 40, 44–47], renal stress [48–55], muscle trauma [34–37, 39, 41, 43, 56, 57], and/or general markers of clinical health/safety [55, 58–65]. Several researchers have also attempted to retrospectively compare the medical status of self-reported creatine users (up to 5 years) to non-users [66, 67]. Other studies have attempted to use questionnaires to assess the prevalence of these potential side effects [38, 68–73]. However, most of these questionnaire based studies did not compare side effects of creatine users to non-creatine using controls and/or attempt to determine whether the side effects commonly reported in the media influenced responses to these questionnaires. Although results of these studies have consistently indicated that creatine supplementation does not appear to cause any of the anecdotally reported side effects, additional long-term research is warranted [1, 2, 26, 27]. The purpose of this study was to examine the short and long-term medical safety of creatine supplementation among athletes in comparison to athletes who did not take creatine during training and competition.

Materials and methods

Subjects

One hundred and sixteen National Collegiate Athletic Association (NCAA) Division IA college football players volunteered to participate in this study over a 2 year period. Subjects were informed as to the experimental procedures and signed informed consent statements in adherence with the Internal Review Board for use of human subjects in research at The University of Memphis and the American College of Sports Medicine. Of these, 98 subjects donated pre- and at least one subsequent blood and urine sample during the course of the study. Descriptively (means ± S.D.), subjects were 19.2 ± 2 years (range 18–23 years), 185 ± 8 cm (range 173–191 cm), 101 ± 18 kg (range 70–148 kg) and included a balanced representation of athletes from each position on the team (i.e. backs, receivers, tight ends, linebackers, lineman, and kickers).

Methods and procedures

Subjects were recruited to participate in this study during pre-season training prior to the 1998 and 1999 seasons. Approximately 65 subjects volunteered to participate during the first year and about 40 subjects volunteered to participate in the second year of the study. All subjects underwent pre-season medical examinations and were cleared to participate in football according to NCAA criteria. Subjects who volunteered to participate in the study chose whether they wanted to take creatine or non-creatine containing supplements during training. Subjects who chose to take creatine were administered in an open label manner 15.75 g/day of creatine monohydrate for 5 days and an average of 5 g/day thereafter in 5–10 g doses following supervised training sessions. Creatine was added to sports drinks or carbohydrate/protein drinks that were offered to players following training sessions, practices, and games by research assistants working with the strength and conditioning staff. Supplement intake was monitored and recorded in order to document creatine intake. When subjects were not on campus, they were provided creatine to take on their own and self-reported compliance. If for some reason a subject fell behind in taking creatine, subjects were administered up to 10 g/day in order to catch them up to an average of 5 g/day.

Fasting blood and 24-h urine samples were collected on as many athletes willing to provide samples at 0, 1, 1.5, 4, 6, 10, 12, 17, and 21 months of training (typically 30–55 per testing session). Collection of blood and urine samples coincided with the athletes reporting for summer school/preseason training (0 months), pre-fall football camp (1 month), post-fall football camp (1.5 months), post-season (4 months), start of spring semester/winter conditioning (6 months), and following spring football practice at the end of the spring semester (10 months) in the first year of supplementation. In the second year, blood and urine samples were obtained prior to fall football camp (12 months), at the end of the football season (17 months), and at of the end of the spring semester (21 months). Subjects who began the study in the second year donated blood and urine samples prior to the fall football season (0 months), after the football season (4 months), and/or at the end of the second semester (9 months).

Training consisted of summer resistance training/conditioning drills (1–2 h/day, 4 days/week), fall football camp (3–6 h/day, 6 days/week), practicing/competing during football season (2–4 h/day, 6 days/week) off-season resistance training/conditioning drills (1–2 h/day, 4 days/week), and spring football practice/resistance training (1–3 h/day, 4–5 days/week). Coaches, athletic trainers, and/or research assistants supervised all training sessions and games. Training duration, type, and general intensity as well as environmental conditions were recorded. Training averaged of 118 ± 68 min per session with an average intensity of 3.3 ± 1 on a 1–5 scale where 1 was equivalent to a walk-through practice prior to games and 5 was equivalent to game competition. Environmental conditions during training and competition ranged from 8–37°C (mean 24.2 ± 8°C) and 20–98% relative humidity (52.2 ± 16%). Injuries and medical conditions treated by athletic training/medical staff were recorded to assess medical status throughout the study. These data were reported in a companion paper presented at the 6th International Meeting on Guanidino Compounds in Biology and Medicine and published in the Journal of Molecular and Cellular Biochemistry [39].

Subjects observed an overnight 8-h fast prior to donating blood samples. Blood samples were obtained via venipuncture from an antecubital vein in the forearm using standard phlebotomy procedures between 6:00–9:00 am during each assessment period. Blood samples were collected into three 10 mL serum separation tubes (SST) and one 5 mL anticoagulant tube containing K3 (EDTA). The SST's were centrifuged at 5,000 rev/min for 10-min using a Biofuge 17R centrifuge (Heraeus Inc., Germany). Serum from two SST was transferred into microcentrifuge tubes and frozen at –80°C for subsequent analysis. Serum from the remaining SST was transferred into a 10 ml plain sterile tube. The plain and EDTA tubes were refrigerated and shipped overnight in cold containers to SmithKline Beecham Clinical Laboratories (Ann Arbor, MI, USA) for standard clinical analysis. A complete metabolic clinical chemistry panel was run on serum samples using the Olympus AU5200 automated chemistry analyzer (Melville, NY, USA) following standard clinical procedures. Cell blood counts with percent differentials and platelet determination were run on whole blood samples using a Coulter STKS automated analyzer using standard procedures (Coulter Inc., Hialeah, FL, USA). These analyzers were calibrated daily to controls according to manufacturers recommendations and federal guidelines for clinical diagnostic laboratories. Test to test reliability of performing these assays ranged from 2–8% for individual assays with an average variation of ±3%. Samples were run in duplicate to verify results if the observed values were outside control values and/or clinical norms according to standard clinical procedures.

Urine samples were collected in 24-h collection containers according to standard procedures. Urine volume was recorded and approximately 10 ml of urine was placed into a urine preservative tube, refrigerated, and shipped overnight in a cold container to SmithKline Beecham Clinical Laboratories to have a 15-item urinalysis performed using the Clinitek Atlas® automated urine chemistry analyzer (Bayer Diagnostics, Tarrytown, NY, USA). This analyzer was calibrated to controls according to manufacturers recommendations and federal guidelines for clinical diagnostic laboratories. In addition, approximately 10 ml of urine was pipetted into a plain sterile transfer tube and stored at –80°C for subsequent analysis. A microcentrifuge of frozen serum and a frozen urine transfer tube was shipped on dry ice to Nichols Institute (San Juan Capistrano, CA, USA) or to the Department of Biomedical Sciences at Queen's Medical Centre (Nottingham, UK) for determination of plasma creatinine, urine creatinine, and creatinine clearance using high performance liquid chromatography (HPLC) according to previously published procedures [6, 52, 53, 55].

Statistical analysis

At the end of the study, subjects were categorized as non-creatine users (n = 44); subjects who took creatine for 0–6 months (mean 4.4 ± 1.8 months, n = 12); subjects who took creatine for 7–12 months (mean 9.3 ± 2.0 months, n = 25); and subjects who took creatine for 12–21 months (mean 19.3 ± 2.4 months, n = 17). The subjects' baseline and final blood and urine samples were analyzed by MANOVA using SPSS for Windows Version 10.05 software (SPSS, Inc., Chicago, IL, USA). In addition, 2 × 2 repeated measures ANOVA univariate tests were performed on all dependent variables. Data were considered statistically significant when the probability of Type I error was 0.05 or less. Data are presented as means ± S.D.

Results

MANOVA revealed no significant differences ($p = 0.51$) between creatine users and non-users in the quantitative panel of blood and urine markers assessed. Since the clinical safety of creatine supplementation is of interest to the scientific and medical community, we have presented the means and standard deviations from the univariate repeated measures ANOVA tests performed on serum metabolic markers, muscle and liver enzymes, electrolytes, blood lipids, hematological markers, and quantitative urinary markers in Tables 1–6, respectively. No significant differences ($p > 0.05$) were observed among groups in any of the quantitative markers analyzed with the exception that significant interactions were observed in sodium, chloride, and hematocrit. However, as Tables 3 and 5 indicate, the differences observed among groups for sodium (141–142 meq/L), chloride (104–105 meq/L), and hematocrit (43–455%) were small, within normal ranges, and therefore do not appear to be of any physiological or clinical significance. No apparent differences were observed among groups in the qualitative urinary assessment of color, appearance, glucose, bilirubin, ketones, hemoglobin, total protein, nitrates, leukocyte esterase, white blood cells, red blood cells, epithelial cells, bacteria, amorphic cyrstals, or calcium oxalate.

Table 1. Metabolic markers for the creatine and non-creatine supplemented subjects. The pre-value is listed at the top and the post value is listed at the bottom of each cell

Variable	Non-creatine control (n = 44)	Creatine 0–6 M (n = 12)	Creatine 7–12 M (n = 25)	Creatine 12–21 M (n = 17)	Univariate interaction
Glucose	87 ± 11	90 ± 14	88 ± 15	84 ± 15	I = 0.16
(mg/dl)	85 ± 6	84 ± 12	84 ± 10	89 ± 9	
Total protein	7.3 ± 0.4	7.2 ± 0.7	7.3 ± 0.03	7.3 ± 0.4	I = 0.15
(g/dl)	7.3 ± 0.3	7.4 ± 0.3	7.2 ± 0.3	7.4 ± 0.4	
Albumin	4.4 ± 0.2	4.4 ± 0.3	4.4 ± 0.2	4.4 ± 0.2	I = 0.37
(g/dl)	4.4 ± 0.2	4.5 ± 0.1	4.4 ± 0.2	4.4 ± 0.2	
Globulin	2.9 ± 0.4	2.9 ± 0.3	2.9 ± 0.3	2.9 ± 0.2	I = 0.55
(g/dl)	2.9 ± 0.4	2.9 ± 0.3	2.8 ± 0.3	3.0 ± 0.3	
Albumin/globulin	1.55 ± 0.3	1.55 ± 0.2	1.56 ± 0.2	1.52 ± 0.2	I = 0.75
ratio	1.53 ± 0.2	1.56 ± 0.1	1.59 ± 0.2	1.48 ± 0.1	
Creatinine	1.23 ± 0.1	1.29 ± 0.2	1.26 ± 0.1	1.16 ± 0.2	I = 0.56
(mg/dl)	1.35 ± 0.1	1.41 ± 0.2	1.42 ± 0.2	1.35 ± 0.2	
Blood urea nitrogen	15.2 ± 3.8	15.2 ± 3.0	15.5 ± 3.8	15.6 ± 3.7	I = 0.85
(BUN) (mg/dl)	15.0 ± 2.9	15.9 ± 3.4	15.2 ± 2.6	15.6 ± 3.5	
BUN/creatinine	12.5 ± 3.3	12.0 ± 2.7	12.5 ± 3.5	13.8 ± 4.4	I = 0.52
ratio	11.2 ± 2.2	11.5 ± 3.1	10.7 ± 1.8	11.7 ± 3.2	
Uric acid	5.5 ± 1.1	5.5 ± 1.0	5.7 ± 1.5	5.3 ± 0.9	I = 0.78
(mg/dl)	5.4 ± 1.1	5.6 ± 1.5	5.5 ± 0.9	4.9 ± 1.0	

Data are means ± S.D.

Table 2. Muscle and liver enzymes for the creatine and non-creatine supplemented subjects. The pre-value is listed at the top and the post value is listed at the bottom of each cell

Variable	Non-creatine control (n = 44)	Creatine 0–6 M (n = 12)	Creatine 7–12 M (n = 25)	Creatine 12–21 M (n = 17)	Univariate interaction
Creatine kinase	796 ± 1124	427 ± 235	579 ± 373	862 ± 1821	I = 0.19
(U/l)	433 ± 146	469 ± 250	659 ± 545	355 ± 248	
Lactate dehydrogenase	180 ± 56	159 ± 91	159 ± 43	177 ± 63	I = 0.33
(U/l)	152 ± 21	151 ± 40	149 ± 38	143 ± 25	
Aspartate aminotransferase	34 ± 24	26 ± 11	28 ± 8	32 ± 22	I = 0.08
(U/l)	27 ± 4	31 ± 19	30 ± 8	25 ± 6	
Alanine aminotransferase	27 ± 11	22 ± 10	28 ± 11	27 ± 14	I = 0.45
(U/l)	25 ± 8	26 ± 13	26 ± 12		
Alkaline phosphatase	91 ± 29	91 ± 23	93 ± 25	101 ± 27	I = 0.09
(U/l)	93 ± 20	94 ± 31	100 ± 19	93 ± 17	

Data are means ± S.D.

Table 3. Serum electrolyte levels for the creatine and non-creatine supplemented subjects. The pre-value is listed at the top and the post value is listed at the bottom of each cell

Variable	Non-creatine control (n = 44)	Creatine 0–6 M (n = 12)	Creatine 7–12 M (n = 25)	Creatine 12–21 M (n = 17)	Univariate interaction
Sodium	141 ± 1	142 ± 3	142 ± 2	141 ± 2	I = 0.01
(meq/L)	141 ± 1	141 ± 1	141 ± 1	140 ± 1	
Chloride	104 ± 2	105 ± 3	105 ± 2	105 ± 2	I = 0.01
(meq/L)	103 ± 2	104 ± 2	103 ± 2	102 ± 2	
Potassium	4.5 ± 0.3	4.6 ± 0.5	4.7 ± 0.6	4.6 ± 0.3	I = 0.33
(meq/L)	4.4 ± 0.3	4.7 ± 0.7	4.5 ± 0.4	4.4 ± 0.2	
Phosphorus	4.3 ± 0.7	4.3 ± 0.6	3.9 ± 0.7	4.1 ± 0.5	I = 0.17
(meq/L)	4.5 ± 0.5	4.1 ± 0.4	4.3 ± 0.5	4.5 ± 0.8	

Data are means ± S.D.

Table 4. Blood lipid profiles for the creatine and non-creatine supplemented subjects. The pre-value is listed at the top and the post value is listed at the bottom of each cell

Variable	Non-creatine control (n = 44)	Creatine 0–6 M (n = 12)	Creatine 7–12 M (n = 25)	Creatine 12–21 M (n = 17)	Univariate interaction
Cholesterol	163 ± 29	174 ± 28	176 ± 27	164 ± 22	I= 0.29
(mg/dl)	172 ± 19	175 ± 22	179 ± 27	180 ± 26	
HDL	47 ± 10	46 ±7	45 ± 10	50 ± 13	I = 0.95
(mg/dl)	48 ± 13	47 ± 6	46 ±7	49 ± 11	
LDL	98 ± 24	111 ± 26	111 ± 22	98 ± 18	I = 0.35
(mg/dl)	106 ± 17	111 ± 22	111 ± 21	108 ± 25	
CHL/HDL	3.6 ± 1.1	3.8 ± 0.7	4.0 ± 0.9	3.5 ± 0.9	I= 0.46
ratio	3.8 ± 1.0	3.8 ± 0.6	4.0 ± 0.9	3.8 ± 0.8	
Triglycerides	92 ± 55	91 ± 40	97 ± 37	83 ± 34	I = 0.19
(mg/dl)	97 ± 44	86 ± 31	108 ± 56	110 ± 48	

Data are means ± S.D.

Discussion

Results of the present study indicate that short and long-term creatine supplementation (up to 21 months) does not appear to adversely effect clinical markers of health status in a large number of athletes undergoing intense training in comparison to athletes who do not take creatine. These findings provide the strongest evidence to date that long-term creatine supplementation does not appear to pose a health risk for athletes. In addition, these findings support previous reports from short-term studies (5 days–12 weeks) and long-term retrospective studies (up to 5 years) that creatine supplementation does not pose a health risk in apparently healthy individuals, athletes, or patient populations [38, 52, 53, 55, 58, 59, 64–66, 74]. The following discusses the results of the present study in consideration of concerns raised regarding the safety of creatine supplementation.

Concerns have been raised that creatine supplementation may increase renal stress and/or impair renal function. These concerns have been primarily fueled by reports of four case studies of possible renal dysfunction in individuals believed to have been taking creatine [75–78]. In each instance, elevations in serum creatinine (e.g. 1.5–1.7 mg/dl) were initially used to diagnose renal stress. Although the conclusions drawn about these case studies have been criticized [63, 79, 80] because these individuals had pre-existing kidney disease [77], may have been misdiagnosed [75], and/or apparently one subject ingested liquid creatine with only 25 mg of creatine per serving indicating that creatine could not have been related to the renal dysfunction observed [78], they have nevertheless raised concerns regarding the long-term safety of creatine supplementation.

Several studies have reported that creatine supplementation during training may increase serum creatinine levels (e.g. from 1.1 to 1.3–1.5 mg/dl). However, since creatine is naturally degraded to creatinine, the increased serum creatinine has been suggested to be due to a greater turnover of creatine following creatine loading and/or due to an ability to maintain a greater training volume/intensity following creatine supplementation [2, 44, 63]. Several recent studies have evaluated the effects of creatine supplementation on renal function by assessing urinary creatinine clearance [31, 48, 51–54] and/or using iohexol infusion techniques to assess glomular filtration [51]. These studies found that creatine

Table 5. Hematological markers for the creatine and non-creatine supplemented subjects. The pre-value is listed at the top and the post value is listed at the bottom of each cell

Variable	Non-creatine control (n = 44)	Creatine 0–6 M (n = 12)	Creatine 7–12 M (n = 25)	Creatine 12–21 M (n = 17)	Univariate interaction
White blood cells	5.5 ± 1.4	5.2 ± 1.0	6.0 ± 1.3	5.4 ± 1.3	I = 0.38
(thous/cum)	5.7 ± 1.0	5.0 ± 0.8	6.0 ± 1.2	5.9 ± 1 1	
Red blood cells	5.0 ± 0.3	4.9 ± 0.2	5.1 ± 0.4	5.0 ± 0.3	I = 0.28
(mil/cum)	5.1 ± 0.3	5.1 ± 0.3	5.1 ± 0.3	5.1 ± 0.3	
Hemoglobin	15.0 ± 1.1	15.0 ± 0.7	15.1 ± 1.0	14.6 ± 0.5	I = 0.22
(g/dl)	15.1 ± 0.9	15.3 ± 0.9	15.3 ± 0.7	15.2 ± 0.5	
Hematocrit	45 ± 3	43 ± 3	45 ± 3	44 ± 2	I = 0.03
(%)	45 ± 2	45 ± 2	46 ± 2	45 ± 1	
Total bilirubin	0.21 ± 0.16	0.22 ± 0.12	0.19 ± 0.01	0.22 ± 0.13	I = 0.22
(mg/dl)	0.16 ± 0.01	0.22 ± 0.01	0.13 ± 0.004	0.14 ± 0.007	
Mean corpuscle	90 ± 5	89 ± 5	88 ± 5	88 ± 4	I = 0.34
volume (fl)	89 ± 4	90 ± 3	89 ± 4	87 ± 4	
Mean corpuscle	30.0 ± 2	30.3 ± 1	29.7 ± 2	29.4 ± 1	I = 0.87
hemoglobin (pg)	30.2 ± 1	30.7 ± 1	29.9 ± 2	29.5 ± 1	
Mean corpuscle	30.6 ± 0.6	34.0 ± 0.6	33.5 ± 0.6	33.4 ± 0.6	I = 0.55
hemoglobin content (%)	33.7 ± 0.6	34.0 ± 0.4	33.5 ± 0.7	33.5 ± 0.7	
Red cell dimension	12.8 ± 0.7	12.3 ± 0.8	12.8 ± 0.8	12.8 ± 0.8	I = 0.86
width (%)	12.6 ± 0.6	12.2 ± 0.7	12.6 ± 0.5	12.6 ± 0.7	
Platelets	223 ± 38	205 ± 30	212 ± 48	226 ± 55	I = 0.89
(thous/cum)	227 ± 34	209 ± 33	219 ± 44	237 ± 51	
Mean platelet volume	9.8 ± 1.0	9.3 ± 1.1	9.9 ± 0.9	10.3 ± 2.9	I = 0.27
(fl)	9.5 ± 0.7	9.1 ± 1.1	10.0 ± 0.9	9.8 ± 1.6	
Neutrophils	47.7 ± 12	48.2 ± 10	51.7 ± 12	51.0 ± 11	I = 0.72
(%)	47.6 ± 10	49.6 ± 5	54.3 ± 9	49.4 ± 7	
Lymphocyges	38.7 ± 11	39.4 ± 11	35.5 ± 11	35.6 ± 9	I=0.36
(%)	39.6 ± 10	37.5 ± 6	33.2 ± 7	38.1 ± 6	
Monocytes	0.48 ± 0.2	0.40 ± 0.2	0.46 ± 0.2	0.44 ± 0.1	I = 0.91
(thous/cum)	0.47 ± 0.2	0.41 ± 0.2	0.44 ± 0.1	0.46 ± 0.1	
Eosonophils	0.24 ± 0.2	0.20 ± 0.1	0.26 ± 0.1	0.22 ± 0.2	I= 0.98
(thous/cum)	0.24 ± 0.1	0.20 ± 0.08	0.27 ± 0.2	0.22 ± 0.1	
Basophils	0.037 ± 0.04	0.040 ± 0.02	0.036 ± 0.03	0.036 ± 0.04	I = 0.59
(thous/cum)	0.034 ± 0.02	0.025 ± 0.02	0.032 ± 0.02	0.043 ± 0.04	
Neutrophil/	1.46 ± 0.9	1.39 ± 0.8	1.71 ± 1.0	1.57 ± 0.6	I = 0.69
lymphocyte ratio	1.32 ± 0.5	1.38 ± 0.4	1.80 ± 0.8	1.36 ± 0.6	

Data are means ± S.D.

Table 6. Quantitative urine markers for the creatine and non-creatine supplemented subjects. The pre-value is listed at the top and the post value is listed at the bottom of each cell

Variable	Non-creatine control (n = 44)	Creatine 0–6 M (n = 12)	Creatine 7–12 M (n = 25)	Creatine 12–21 M (n = 17)	Univariate interaction
Volume	1.50 ± 0.6	1.38 ± 0.8	1.67 ± 0.7	1.38 ± 0.5	I = 0.38
(l)	1.22 ± 0.3	1.05 ± 0.4	1.27 ± 0.6	1.37 ± 0.7	
Specific gravity	1.023 ± 0.006	1.024 ± 0.009	1.020 ± 0.006	1.019 ± 0.005	I = 0.24
	1.026 ± 0.004	1.024 ± 0.007	1.025 ± 0.005	1.025 ± 0.007	
pH	6.3 ± 0.6	6.1 ± 0.5	6.3 ± 0.6	6.1 ± 0.4	I = 0.36
	6.1 ± 0.3	6.2 ± 0.4	6.2 ± 0.4	6.1 ± 0.6	
Creatinine	2 .82 ± 1.6	2.45 ± 1.36	2.55 ± 1.2	2.67 ± 1.1	I = 0.76
(g/24 h)	2.30 ± 0.9	2.13 ± 0.8	2.47 ± 1.2	2.27 ± 1.8	
Creatinine clearance	269 ± 241	171 ± 117	234 ± 165	213 ± 150	I = 0.69
(ml/min)	162 ± 100	120 ± 63	168 ± 165	177 ± 185	

Data are means ± S.D.

supplementation has no apparent impact on renal function. Results of the present study support these findings in that no significant differences were observed among creatine and non-creatine users in serum creatinine, urinary creatinine excretion, or creatinine clearance.

Interestingly, baseline creatinine levels in the present study were at the upper end of normal for untrained individuals in all groups (i.e. 0.5–1.2 mg/dl) and the post-values were above normal values (1.35–1.42 mg/dl) in all groups. Although no significant differences were observed among creatine users and controls, most athletes had serum creatinine levels between 1.2–1.7 mg/dl particularly during more intense training periods. If one only used serum creatinine to diagnose renal stress, one could infer that many of these athletes were experiencing renal stress (regardless of whether they were taking creatine or not). Yet, no significant differences were observed among groups in creatinine clearance and values were within or exceeded norms (i.e. > 75–150 ml/min). It is also interesting to note that baseline creatinine clearance values (typically obtained prior to fall football season) were above norms (171–269 ml/min) and that post creatinine clearance values analysis (typically obtained at the end of the football season or at the end of the second academic semester) decreased in all groups from pre- to post analysis (suggesting a decreased renal function) but remained within or slightly above clinical norms (120–177 ml/min). These findings indicate that renal function may vary among college football players possibly due to their large body mass and/or the type and volume of training they are engaged. Consequently, it is our view that care must be taken when interpreting individual changes in serum creatinine and/or creatinine clearance in these types of athletes and inferring that creatine supplementation may have been related to changes in these renal markers when large variations in these variables are apparently normal for this population.

Concerns have also been raised that creatine supplementation may increase muscle and/or liver damage [2, 27, 55]. This concern has been based on an initial report suggested that athletes taking creatine during training may experience slightly elevated muscle and/or liver enzymes [44]. Although the levels reported were within normal values for athletes, some have suggested that creatine may increase muscle and/or liver damage. Results of the present study indicated that athletes engaged in intense training have creatine kinase (CK) levels above clinical norms for untrained individuals (i.e. > 225 IU/L). However, the mean values observed were within normal ranges for athletes engaged in intense training (i.e. typically 250–1,000 IU/L) and no significant differences were observed among creatine and non-creatine users in CK values. In addition, no significant differences were observed among creatine and non-creatine supplemented groups in lactate dehydrogenase (LDH), aspartate aminotransferase (AST), or alanine aminotransferase (ALT) values and all of these values were within normal ranges (i.e. LDH 100–250; AST and ALT < 55 IU/L) for non-athletes. These findings indicate that although these athletes may have had elevated CK levels, there does not appear to be any difference in muscle and liver enzyme efflux among athletes who do and do not take creatine during intense training and competition.

Creatine supplementation has also been suggested to alter fluid balance and/or electrolyte status. The basis of this concern was from initial reports suggesting that urine output may decrease slightly during creatine loading thereby suggesting that short-term creatine supplementation may increase fluid retention [6]. Although subsequent studies have been unable to demonstrate a disproportionate increase in total body water following creatine supplementation [31, 40, 44, 46], the potential increase in fluid retention has been theorized to dilute electrolytes and predispose athletes to cramping. Results of the present study do not support this hypothesis. Although significant interactions were observed among groups in sodium and chloride levels, differences among groups were negligible (i.e. < 1 meq/L) and of no physiological or clinical significance. In addition, no significant differences were observed among groups in potassium, calcium, phosphorus, urine output, or urine specific gravity. Moreover, as reported in our companion paper to this study, creatine supplementation did not increase the incidence of dehydration or muscle cramping in these athletes monitored over a 3-year period [39]. These findings support results of previous studies indicating that creatine supplementation does not increase thermal stress or promote dehydration [29–33, 46, 47, 81], cramping [31, 34–43], or alter electrolyte status [31, 40, 44, 45].

Earnest and colleagues [82] reported that creatine supplementation lowered blood lipids in a group of subjects with high triglycerides. Since then, several researchers have examined whether creatine supplementation affects blood lipid profiles [44, 83–85]. One theory for this phenomenon is that creatine supplementation may enhance the quality of training thereby accentuating the positive effects of exercise on blood lipid profiles. Potentially, a creatine induced reduction in cholesterol and/or triglyceride levels may have significant health benefits. Although we previously reported that blood lipid profiles were improved during the initial 42-days of this study as subjects went through pre-season training and football camp [86], no significant differences were observed among creatine and non-creatine users in our one-year analysis [62] or in the present overall analysis. These findings suggest that the possible influence of creatine on lipid profiles in athletes with normal blood lipids is either transient or non-existent. Present findings support other reports indicating creatine supplementation does not appear to affect blood lipid levels in athletes [55, 67, 84, 85]. However, additional research should examine the potential influence of creatine supplementation on lipid profiles particularly in individuals with elevated cholesterol and/or triglycerides.

The last major concern about creatine supplementation that we would like to address is that creatine supplementation may cause unknown long-term side effects. Results of the present study do not support these contentions. In this regard, we saw no evidence that short- or long-term creatine supplementation caused any clinically significant change in serum metabolic markers, muscle and liver enzyme efflux, serum electrolytes, blood lipid profiles, red and white whole blood cell hematology, or quantitative and qualitative urinary markers. These findings support other reports indicating that long-term creatine supplementation (up to 5 years) did not appear to cause clinically significant side effects in various patient populations and/or retrospective analysis of athletes [52, 55, 64–66]. Although research should continue to evaluate the health consequences of creatine supplementation (particularly in adolescents and various patient populations), results of this study indicate that creatine supplementation (~ 5 g/day for up to 21 months) appears to be a safe nutritional supplement for athletes engaged in intense training and competition.

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