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ORIGINAL CONTRIBUTION

Helmut Schröder
Nicolas Terrados
Antonio Tramullas

Risk assessment of the potential side effects of long-term creatine supplementation in team sport athletes

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H. Schröder, PhD (✉)
Lipids and Cardiovascular Epidemiology Unit
Institut Municipal d'Investigació Mèdica, IMIM
c/Doctor Aiguader 80
08003 Barcelona, Spain
E-Mail: hschroeder@imim.es

H. Schröder
Sports Medicine Barcelona
Dept. of Nutrition
Barcelona, Spain

N. Terrados
Fundación Deportiva Municipal de Avilés
Oviedo, Spain

N. Terrados
Dept. of Functional Biology
University of Oviedo
Oviedo, Spain

A. Tramullas
Sports Medicine Barcelona
Dept. of Sports Medicine
Barcelona, Spain

A. Tramullas
Medical Services Football Club Barcelona
Barcelona, Spain

A. Tramullas
Medical Services Hospital de Asepeyo
Sant Cugat, Spain

Summary *Background* Use of creatine has become widespread among sportsmen and women, although there are no conclusive evidences concerning possible health risks of long-term creatine supplementation. *The aim of the study* To investigate long-term effects of creatine monohydrate supplementation on clinical parameters related to health. *Methods* Eighteen professional basketball players of the first Spanish Basketball League participated in the present longitudinal study. The subjects were ingesting 5 g creatine monohydrate daily during three competition seasons. Blood was collected in the morning after an overnight fast, five times during each of the three official competition seasons of the first National Basketball League (September 1999–June 2000, September 2000–June 2001 and September 2001–June 2002) and the European League. Standard clinical examination was performed for 16 blood chemistries. *Results* The plasma concentrations of all clinical parameters did not alter significantly during the analyzed time frames of creatine supplementation. All of these parameters were, with the exception of creatinine and creatine kinase, within their respective clinical ranges at all time points. *Conclusion* Our data shows that low-dose supplementation with creatine monohydrate did not produce laboratory abnormalities for the majority of the parameters tested.

Key words nutrition – exercise – adverse effects – elite athletes – health

Introduction

In recent years, creatine supplementation has received great attention in both popular and scientific media. There are numerous studies and reviews examining the efficacy of creatine as an ergogenic aid. The weight of scientific evidence indicates that creatine supplementation increases physical performance [1–3], overall high-intensity performance lasting 30-s or less, especially if performance is repeated a number of times [4–6]. The benefits of creatine supplementation on exercise performance have been extended as a possible therapeutic agent in the treatment of disease conditions [4, 7–9].

The sporting world has recognized the ergogenic effects of creatine, and hence, the use of creatine has become widespread in recent years [10, 11]. However, in contrast to the amount of information available on the effects of creatine supplementation on physical

performance, the data on possible health risks of this supplementation practice is limited.

As drug abuse in professional athletes has become more public, interest has focused on the harmful effects of ergogenic supplements. However, to date the only documented side effects resulting from creatine supplementation have been weight gain, which may be partially associated with water retention [3, 4], and an increase in anterior compartment pressures in the lower leg [12]. Few controlled studies have directly examined side effects [13–18], and most long-term studies were of retrospective nature (1518). Thus far, there is limited information of longitudinal studies on side effects of regular creatine supplementation in professional sport.

Therefore, the aim of the present study was to analyze the effects of creatine supplementation during one, two and three competition seasons on several clinical parameters in healthy highly trained professional athletes.

Subjects and methods

Subjects

Eighteen professional male basketball players were recruited for the present study from a top-level European basketball team. This team competes in the first Spanish Basketball League (ACB) and at international level in the European League. Subjects were informed about procedures and possible risks involved before giving their voluntary consent to participate. The protocol was approved by the Research Ethics Committee of the University of Oviedo, Spain. The study started in September 1999 and finished in June 2002 (Fig. 1).

Methods

Data collection and analysis

Anthropometrical data (age, height, mass and body mass index) of the participants was recorded. Body mass index was calculated as weight divided by squared height (kg/m^2). Venous blood samples were taken from superficial forearm veins. Blood samples were collected in the morning between 9:00 and 11:00 after an overnight fast without venous compression. The last training load was completed around 16 hours before blood collection. Blood was drawn for data analysis 15 times during the entire study. Blood chemistry parameters were collected one time during each pre-competition and four times during each competition season (Fig. 1). Standard clinical analysis was performed for 16 selected clinical parameters (Total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, creatinine, uric acid, urea, serum glutamic oxalactic transaminase, serum glutamic pyruvic transaminase, gamma glutamyl transpeptidase, alkaline phosphotase, lactate dehydrogenase, creatine kinase, potassium, magnesium, and phosphate). Data of these variables were available from 18 participants for 1 competition season, for 12 participants for two consecutive pre- and competition seasons and for 6 participants during the entire time frame of the study. All laboratory measurements were performed by an official and certified clinical laboratory (LAT, S. A., Barcelona, Spain; ISO number: UNE-EN-ISO-9001: 2000). Packed cell volume and hemoglobin concentration were measured on whole blood at all time points to correct for exercise induced plasma volume shifts using the equations of Dill and Costill [19].

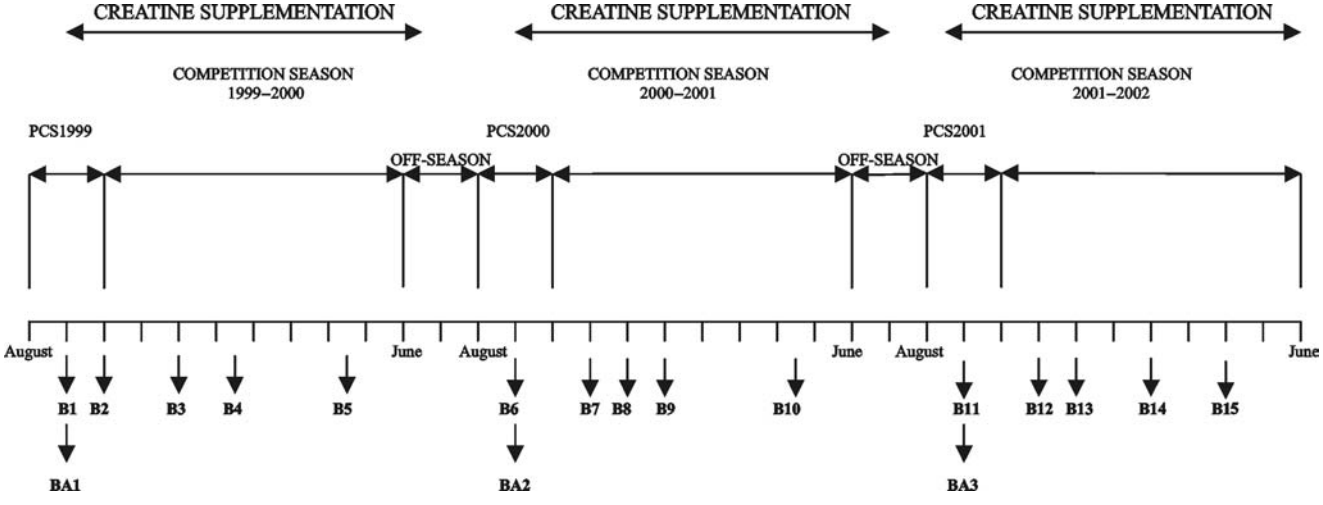

Fig. 1 Time points of blood collection (*B* Blood collection for data analyses; *PCS* Pre-competition season; *BA* Baseline)

Creatine supplementation

All participants received a daily loading dosage of 20 g of creatine monohydrate (Creatine®, Nutrisport, Barcelona Spain) for five days consecutively in pre-competition seasons. Maintenance dosage of creatine supplementation during entire competition seasons was 5 g/d (Fig. 1). The creatine supplement was administered through the team physician who thereby controlled compliance of supplement intake. Participants did not consume creatine during each off- and the first half of the pre-competition season. Hence, there are three baseline time points (Fig. 1). The present time pattern of supplementation is characteristic for team sports that normally includes a six to eight week off season. No control group was included because the aim of the study was to analyze the absolute risk (represented through upper limits of clinical markers) and not the relative risk of creatine supplementation. Furthermore, it is difficult, if not impossible, to recruit professional basketball players for a control group which did not receive a potentially performance enhancing supplement over 3 years. The athletes consumed daily on average around 100 g of a carbohydrate/protein mixture and an antioxidant supplement containing (200 mg vitamin C and 100 mg vitamin E).

Statistical analysis

Analysis of means by independent samples T test (GLM) was used to calculate the main characteristics of the participants. Analysis of variance (ANOVA) for multiple measurements was used to calculate the effects of creatine supplementation on clinical variables across several time points. ANOVA for 1, 2 and 3 competition seasons included 18, 12 and 6 subjects and 5 (Fig. 1: B1–B5), 10 (Fig. 1: B1–B10) measurements respectively. To calculate side effects of creatine supplementation over 3 competition seasons we analyzed blood chemistries data at time points B1, B5, B7, B10, and B14 (Fig. 1). Analyses of the data were conducted using SPSS for Windows (version 9.0) statistical software package (SPSS Inc, Chicago, IL). In all statistical analyses, P values of < 0.05 were considered significant.

Results

Anthropometrical data of the participants are shown in Table 1. The effect of creatine supplementation over 1 to 3 competition seasons of the first Spanish Basketball League (September 1999–June 2002) on indices of muscle damage and hepatic and renal function are shown in Tables 2, 3, and 4, respectively. Average values of these

Table 1 Physical characteristics of the subjects

Parameter	n = 18
Age (years)	24±4
Height (cm)	204±10
Body mass (kg)	101±14
Body mass index (BMI)	24.2±1.9

n number of subjects

Table 2 Clinical parameters of 18 male, creatine-supplemented, basketball players during one entire competition season

Parameter	Variable	Unit	B1	B2	B3	B4	B5	P for linear trend
Blood	Creatinine	$\mu mol \cdot L^{-1}$	123±12	112±10	119±11	115±8	122±9	NS
	Urea	$mmol \cdot L^{-1}$	6.7±1.6	6.1±1.4	6.4±1.5	6.4±1.5	7.2±1.3	NS
	Uric acid	$mmol \cdot L^{-1}$	348±58	301±55	340±50	308±60	324±66	NS
Minerals	Potassium	$mmol \cdot L^{-1}$	3.8±0.1	4.0±0.4	4.0±0.5	4.0±0.4	3.9±0.5	NS
	Calcium	$mmol \cdot L^{-1}$	2.4±0.1	2.3±0.2	2.4±0.2	2.3±0.2	2.4±0.2	NS
	Magnesium	$mmol \cdot L^{-1}$	0.9±0.1	0.9±0.1	0.9±0.1	0.9±0.1	0.8±0.1	< 0.01
Lipids	TC	$mmol \cdot L^{-1}$	4.3±0.6	4.1±0.6	4.4±0.6	4.1±0.7	4.3±0.7	NS
	LDL-C	$mmol \cdot L^{-1}$	2.5±0.6	2.8±0.9	2.6±0.6	2.3±0.6	2.5±0.6	NS
	HDL-C	$mmol \cdot L^{-1}$	1.5±0.3	1.4±0.2	1.4±0.3	1.4±0.3	1.4±0.2	NS
	Triglycerides	$mmol \cdot L^{-1}$	0.9±0.2	0.8±0.3	0.8±0.3	0.8±0.3	0.9±0.3	NS
Serum Enzymes	LDH	$IU \cdot L^{-1}$	307±79	319±57	332±57	321±51	349±54	NS
	SGOT	$IU \cdot L^{-1}$	27.2±7.2	25.6±8.4	29.9±7.4	26.1±7.3	29.7±9.2	NS
	SGPT	$IU \cdot L^{-1}$	21.9±6.1	23.2±7.4	24.6±6.4	22.8±6.6	21.0±8.9	NS
	GGT	$IU \cdot L^{-1}$	16.5±6.2	15.4±5.7	15.4±4.6	14.7±4.8	15.3±5.3	NS
	ALK PHOS	$IU \cdot L^{-1}$	237±57	209±50	240±72	202±40	209±37	NS
	CK	$IU \cdot L^{-1}$	398±253	301±350	316±157	263±131	405±255	NS

TC total cholesterol; *LDL-C* low density lipoprotein cholesterol; *HDL-C* high density lipoprotein cholesterol; *LDH* lactate dehydrogenase; *SGOT* serum glutamic oxalactic transaminase; *SGPT* serum glutamic pyruvic transaminase; *GGT* gamma glutamyl transpeptidase; *ALK PHOS* alkaline phosphatase; *CK* creatine kinase; *NS* not significant; *B* blood collection

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Table 3 Clinical parameters of 12 male, creatine-supplemented, basketball players during two entire competition seasons

Parameter	Variable	Unit	B1	B2	B3	B4	B5	B6	B7	B8	B9	B10	P for linear trend
Blood	Creatinine	µmol·L^{-1}	127±10	112±12	115±8	114±8	117±8	118±10	115±10	124±38	116±10	117±13	NS
	Urea	mmol·L^{-1}	7.6±1.1	6.5±1.5	6.8±1.5	7.0±1.5	7.3±1.2	7.0±1.1	7.0±1.3	6.7±2.0	6.8±1.4	6.9±1.1	NS
	Uric acid	mmol·L^{-1}	359±66	293±111	340±63	290±63	328±76	329±64	290±70	308±95	348±74	306±75	NS
Minerals	Potassium	mmol·L^{-1}	3.8±0.1	4.1±0.4	4.0±0.5	4.0±0.5	3.9±0.5	3.9±0.2	4.0±0.3	4.1±0.7	4.1±0.3	3.9±0.5	NS
	Calcium	mmol·L^{-1}	2.4±0.1	2.3±0.2	2.5±0.2	2.4±0.3	2.4±0.2	2.4±0.1	2.4±0.3	2.4±0.3	2.5±0.2	2.2±0.3	NS
	Magnesium	mmol·L^{-1}	0.9±0.1	0.9±0.1	0.9±0.1	0.8±0.1	0.9±0.1	0.9±0.1	0.8±0.1	0.8±0.1	0.8±0.1	0.8±0.1	< 0.0001
Lipids	TC	mmol·L^{-1}	4.5±0.6	4.2±0.6	4.5±0.7	4.2±0.7	4.3±0.8	4.3±0.9	4.4±0.9	4.3±1.0	4.4±0.8	4.2±0.8	NS
	LDL-C	mmol·L^{-1}	2.7±0.5	2.6±1.2	2.7±0.6	2.5±0.6	2.6±0.7	2.5±0.6	2.3±0.5	2.6±0.8	2.7±0.8	2.5±0.8	NS
	HDL-C	mmol·L^{-1}	1.4±0.2	1.4±0.3	1.4±0.3	1.4±0.3	1.3±0.2	1.3±0.3	1.4±0.3	1.4±0.3	1.5±0.3	1.3±0.2	NS
	Triglycerides	mmol·L^{-1}	0.9±0.2	0.8±0.3	0.7±0.3	0.8±0.3	0.9±0.3	0.8±0.3	1.0±0.4	0.8±0.3	0.7±0.3	0.8±0.2	NS
Serum	LDH	IU·L^{-1}	318±77	336±57	337±60	329±53	341±58	325±60	302±67	307±55	324±76	323±27	NS
Enzymes	SGOT	IU·L^{-1}	28.3±8.1	26.0±10.3	30.9±8.7	26.1±8.3	28.3±10.2	26.2±6.7	27.4±4.3	30.7±10.3	29.0±6.3	27.5±8.0	NS
	SGPT	IU·L^{-1}	19.9±5.2	21.9±8.0	23.6±6.7	20.9±6.0	18.6±7.6	23.2±9.9	20.7±5.6	25.8±8.1	22.7±6.9	22.7±8.2	NS
	GGT	IU·L^{-1}	14.1±3.5	13.5±4.6	13.9±3.4	12.2±3.1	13.1±2.7	14.5±4.1	15.4±4.1	12.0±3.3	14.6±4.5	14.2±3.1	NS
	ALK PHOS	IU·L^{-1}	264±56	223±56	237±65	216±44	214±41	223±36	209±29	172±23	210±33	196±28	< 0.0001
	CK	IU·L^{-1}	394±277	392±404	312±179	266±144	358±231	400±394	364±380	391±388	392±368	434±176	NS

TC total cholesterol; *LDL-C* low density lipoprotein cholesterol; *HDL-C* high density lipoprotein cholesterol; *LDH* lactate dehydrogenase; *SGOT* serum glutamic oxalactic transaminase; *SGPT* serum glutamic pyruvic transaminase; *GGT* gamma glutamyl transpeptidase; *ALK PHOS* alkaline phosphatase; *CK* creatine kinase; *NS* not significant; *B* blood collection

parameters were, with the exception of creatinine and creatine kinase, within their normal clinical ranges (Tables 2, 3 and 4).

The average creatine kinase serum activities of the participants were above the upper clinical reference value (normal range: 0–190 IU) at all time point. This was observed for creatinine plasma concentrations only before starting with creatine supplementation of the first competition season (Table 2, Fig. 1). There were no significant differences in activity or concentration of the clinical parameters among all time points. Furthermore, creatine supplementation did not significantly increase the concentrations or activities of the parameters during the analyzed time frames. On the contrary, an inverse linear trend was observed for magnesium concentration and alkali phosphatase activity.

Discussion

This longitudinal study sought to investigate the effects of creatine loading and low dose supplementation on several markers of hepatic and renal function and muscle damage, during three competition seasons of the first Spanish Basketball League. With the exception of creatinine and creatine kinase, we found all of these clinical parameters within their respective normal clinical range at all measured time points.

The dosage of creatine supplementation was constant (5 g/d after the loading period of 20 g during one week) during the entire study period and it is comparable with that of previous studies. Furthermore, this low-dose supplementation of creatine is recommended by creatine manufacturers. There is evidence that supplementation with creatine increases physical performance, that is, overall high-intensity performance lasting 30-s or less [4–6], although controversial results have been reported [20]. Furthermore, there are some in-field studies indicating favorable effects of creatine supplementation on performance [21–23].

Concerns have been raised that creatine supplementation may increase muscle or liver damage [20]. The release of cytosolic enzymes into the extracellular space can be associated with liver dysfunction and muscle injury. Therefore, it is reasonable to assume that the adverse effects of creatine supplementation, if any, would alter plasma concentrations or activity of these clinical markers with long-term administration.

Serum activities of creatine kinase, an unspecific muscle damage marker, increases after exercise and elevated serum activities of this enzyme remained high during several days after exercise [24, 25]. In the present study, we observed abnormally high clinical activities of creatine kinase at all measured time points. However, there was no increasing trend of creatine kinase serum activities during the time of creatine supplementation.

Table 4 Clinical parameters of 6 male, creatine-supplemented, basketball players during three entire competition seasons

Parameter	Variable	Unit	B1	B5	B7	B10	B14	P for linear trend
Blood	Creatinine	$\mu mol \cdot L^{-1}$	125±12	115±10	115±13	117±5.5	112±13	NS
	Urea	$mmol \cdot L^{-1}$	7.2±0.9	7.3±0.9	5.9±0.2	7.1±0.9	6.5±0.9	NS
	Uric acid	$mmol \cdot L^{-1}$	357±70	306±56	332±69	301±69	285±72	NS
Minerals	Potassium	$mmol \cdot L^{-1}$	3.8±0.1	3.8±0.6	4.0±0.1	3.8±0.4	4.0±0.4	NS
	Calcium	$mmol \cdot L^{-1}$	2.4±0.1	2.3±0.2	2.3±0.1	2.4±0.3	2.4±0.2	NS
	Magnesium	$mmol \cdot L^{-1}$	0.8±0.1	0.7±0.1	1.0±0.1	0.8±0.1	0.9±0.1	NS
Lipids	TC	$mmol \cdot L^{-1}$	4.6±0.7	4.3±0.4	4.2±0.5	4.4±0.7	4.4±0.3	NS
	LDL-C	$mmol \cdot L^{-1}$	2.8±0.5	2.6±0.4	2.7±0.5	2.5±0.4	2.8±0.5	NS
	HDL-C	$mmol \cdot L^{-1}$	1.4±0.3	1.3±0.2	1.2±0.1	1.3±0.2	1.4±0.3	NS
	Triglycerides	$mmol \cdot L^{-1}$	0.8±0.2	0.9±0.3	0.7±0.1	0.9±0.2	1.0±13	NS
Serum Enzymes	LDH	$IU \cdot L^{-1}$	268±49	322±26	310±59	269±32	315±45	NS
	SGOT	$IU \cdot L^{-1}$	26.8±2.2	26.7±7.1	25.2±7.9	24.0±4.7	30.1±13.4	NS
	SGPT	$IU \cdot L^{-1}$	18.2±3.6	15.4±4.9	18.7±7.7	19.8±6.5	22.7±11.1	NS
	GGT	$IU \cdot L^{-1}$	15.0±3.5	13.5±3.3	13.5±3.5	14.2±3.2	14.7±3.3	NS
	ALK PHOS	$IU \cdot L^{-1}$	249±22	207±33	254±20	203±25	235±28	NS
	CK	$IU \cdot L^{-1}$	356±140	308±167	288±192	395±119	323±284	NS

TC total cholesterol; *LDL-C* low density lipoprotein cholesterol; *HDL-C* high density lipoprotein cholesterol; *LDH* lactate dehydrogenase; *SGOT* serum glutamic oxalactic transaminase; *SGPT* serum glutamic pyruvic transaminase; *GGT* gamma glutamyl transpeptidase; *ALK PHOS* alkaline phosphatase; *CK* creatine kinase; *NS* not significant; *B* blood collection

Furthermore, we had previously observed similar creatine kinase activity patterns in non-creatine supplemented professional basketball players [26]. Therefore, habitually high activities of creatine kinase observed in these athletes probably might be a consequence of the large amounts of eccentric loads rather than a side effect of creatine supplementation. Furthermore liver damage marker, including serum glutamic oxalatic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), and gamma glutamyl transpepdidase (SGGT) were in their normal clinical ranges and did not increase among time points. Hence, results of the present study suggests that long-term creatine supplementation is not a risk factor for muscle or liver damage.

Several case studies reported renal dysfunction in individuals believed to have been taken creatine [27, 28]. Hence, concerns have been raised that creatine increase renal stress or might conduct to renal dysfunction. Alterations of serum concentrations of creatinine, urea, magnesium, calcium, and potassium are associated with kidney pathology [29]. The kidney plays a crucial role in creatine metabolism as it accomplishes urinary excretion of creatinine, the end product of creatine metabolism [7]. An increase in urinary creatinine excretion accompanies creatine supplementation. Hence, it would be expected that creatine supplementation increases plasma creatinine concentration. Indeed, although not usually exceeding the upper clinical reference value, we observed high creatinine plasma concentrations. However, the regular and high-intensity training loads performed by the participants may induce protein degradation and thus lead to an increase in plasma creatinine. Furthermore, we did not detect an increase in plasma concentrations of creatinine during three competition seasons of creatine supplementation. Electrolyte homeostasis is essential for health and a disturbance of this balance can conduct to severe clinical conditions. In the present study there were no alterations in plasma concentrations of magnesium, potassium, and calcium. Because electrolyte imbalance can be considered as an indirect indicator for renal dysfunction, our results suggest that creatine supplementation did not affect renal function over the entire study period, which is in line with previous findings [13–18]. However, we cannot completely exclude adverse side effects of creatine supplementation on renal function because we did not measure kidney function parameters. More prospective studies, ideally including kidney function parameters, are necessary to address this important issue.

The imbalance of the electrolyte status, particular potassium, is important in the pathogenesis of cardiovascular disease and sudden cardiac death [30]. Importantly, sudden cardiac death affects several young sportsmen for yet unknown reasons every year. Plasma potassium values were constant, and in the normal clinical range, among all time points in the present study. Hence, it can be assume that creatine supplementation does not exert adverse effects on potassium homeostasis.

The present study was designed to analyze effects of creatine supplementation under realistic conditions in professional sport. This includes an off-season, typically

for most sports. Since wash-out time for creatine is 4–6 weeks [31], and participants had a 2 month off-season without consuming creatine, there was sufficient time for creatine to be eliminated from their bodies. This could be considered a weakness of the study concerning long-term effects over two years of creatine supplementation. On the other hand, as stated above, most sports include off-seasons and wash-out of creatine during this period is probable. Furthermore, a wash-out period eliminates creatine, but might not be sufficient to reverse adverse subclinical effects, not detectable during one entire season of creatine supplementation. The risk of clinical manifestation of adverse effects might be more probable after restarting with creatine supplementation after two months of washing-out than abstinence of creatine use.

In conclusion, supplementation with creatine did not alter clinical indices related to hepatic and renal pathology or muscle injury. Low dose creatine supplementation seems to be safe in healthy young athletes for the time frame of the present study. However, regular clinical monitoring of athletes is recommended in the case of long-term creatine usage.

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