

# Dietary creatine supplementation does not affect some haematological indices, or indices of muscle damage and hepatic and renal function

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## Abstract

**Background**—The use of creatine (Cr) as a nutritional supplement to aid athletic performance has gained widespread popularity among athletes. However, concerns have recently been expressed over potentially harmful effects of short and long term Cr supplementation on health. **Methods**—Forty eight young healthy subjects were randomly allocated to three experimental protocols aimed at elucidating any potential health risks associated with five days (20 g/day) to nine weeks (3 g/day) of Cr supplementation. Venous blood samples were collected before and after periods of Cr supplementation and were analysed for some haematological indices, and for indices of hepatic, muscular, and renal dysfunction.

**Findings**—All measured indices were well within their respective normal range at all times. Serum creatinine concentration tended to be increased the day after Cr supplementation. However, values had returned to baseline six weeks after the cessation of supplementation. These increases were probably attributable to increased creatinine production rather than renal dysfunction. No indication of impairment to the haematological indices measured, hepatic function, or muscle damage was apparent after Cr supplementation.

**Interpretation**—These data provide evidence that there are no obvious adverse effects of acute or more chronic Cr supplementation on the haematological indices measured, nor on hepatic, muscle, and renal function. Therefore there is no apparent health risk associated with Cr supplementation to healthy people when it is ingested in quantities that have been scientifically proven to increase muscle Cr stores.

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Keywords: creatine supplementation; kidney; liver; blood; muscle; exercise; metabolism

Creatine (Cr) metabolism is of interest because of its pivotal role in energy transduction in cells with fluctuating energy demands. Current interests in Cr as a nutritional supplement include its use as an ergogenic aid<sup>1</sup> and its potential therapeutic role in conditions such as cardiac insufficiency.<sup>2</sup> In recent years Cr supplementation has been shown by several

laboratories to have a positive effect on the performance of repeated bouts of short lasting maximal exercise,<sup>1–5</sup> the magnitude of which has been associated with the extent of muscle Cr accumulation.<sup>5</sup> As a result, Cr has become a very popular dietary supplement used by amateur and professional athletes, with sales in the United States totalling \$100m (£60m) during 1997.<sup>6</sup>

In most studies, a dosing regimen of 20 g Cr a day for five days<sup>7–8</sup> has been used to “load” muscles with Cr. The single 5 g dose used in this regimen can increase plasma Cr concentration by up to 13-fold, which then remains significantly higher than basal concentration for three hours.<sup>9</sup> It is believed that this promotes the transport of Cr into muscle and, after five days of supplementation, results in about a 25 mmol/kg dry mass increase in muscle total Cr (TCr). The muscle TCr concentrations achieved by this regimen can be maintained by continuing Cr ingestion at a “maintenance dose” of about 2 g every day,<sup>8</sup> which represents the average rate of daily Cr degradation to creatinine.<sup>10</sup>

Anecdotal opinions have been expressed<sup>6–11</sup> about the potential effect of ingested Cr on aspects of health, such as muscle cramping, muscle-tendon injury, and renal dysfunction. Opinions such as these, however, have not been supported with scientific evidence, other than two recent case reports of renal dysfunction accompanying oral creatine supplementation,<sup>12–13</sup> one of which was in a patient with pre-existing kidney disease.<sup>12</sup> Despite its apparent widespread use by athletes,<sup>14</sup> there is little published evidence of the effects of Cr supplementation on health indices, such as haematological, hepatic, and renal function, or muscle damage. The aim of this study therefore was to obtain information on such indices in young healthy adult subjects, before and after a typical regimen of “Cr loading”, and also after a typical Cr loading and eight week “maintenance” regimen.<sup>8</sup>

## Methods

### SUBJECTS

Forty eight healthy subjects volunteered to take part in the series of experiments. None reported any history of kidney or liver related illness. All subjects regularly undertook some form of exercise but none was highly trained. Before inclusion, informed written consent was obtained from all of them, and ethical approval was obtained from the Nottingham University Medical School ethics committee.

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Table 1 Summary of experimental groups and protocol

Experimental group	No and sex	Summary of treatment	Time of sampling after supplementation
Cr <sub>LOAD</sub>	7, men	5 g Cr + 500 ml CHO drink, 4 times daily, 5 days	1 day
P <sub>LOAD</sub>	7, men	500 ml CHO drink, 4 times daily, 5 days	1 day
Cr <sub>LOAD+6</sub>	6, men	5 g Cr + 1 g glucose, 4 times daily, 5 days	6 weeks
P <sub>LOAD+6</sub>	6, 3 men, 3 women	6 g glucose, 4 times daily, 5 days	6 weeks
Cr <sub>MAINT</sub>	7, women	5 g Cr, 4 times daily, 5 days followed by 3 g Cr daily, 8 weeks	1 day
Cr <sub>MAINT+EX</sub>	9, women	5 g Cr, 4 times daily, 5 days followed by 3 g Cr daily, 8 weeks + resistance exercise training	1 day
P <sub>MAINT+EX</sub>	6, women	5 g glucose, 4 times daily, 5 days followed by 3 g glucose daily, 8 weeks + resistance exercise training	1 day

CHO, carbohydrate.

#### EXPERIMENTAL GROUPS

The 48 subjects were divided randomly into seven experimental groups to examine two different aspects of Cr supplementation (table 1).

#### Effects of a Cr loading regimen

Group Cr<sub>LOAD</sub> consisted of seven men (mean (SD) age 23 (4) years and body mass index (BMI) 22.4 (2.1) kg/m<sup>2</sup>) who ingested 5 g Cr dissolved in a warm drink followed by 500 ml of a carbohydrate-containing solution four times a day for five days. This regimen was used because we have previously shown it to augment muscle Cr accumulation by about 60% more during five days of Cr loading than when Cr alone was ingested.<sup>15</sup> This increase in Cr accumulation has been attributed to insulin augmenting sodium dependent muscle Cr transport.<sup>15</sup> Blood samples for analysis were obtained the day before supplement ingestion began and the day after the ingestion regimen had been completed.

Group P<sub>LOAD</sub> (a placebo group) consisted of seven men (age 24 (5) years; BMI 21.3 (0.9) kg/m<sup>2</sup>) who ingested 500 ml of a carbohydrate-containing solution four times a day for five days. Blood samples for analysis were obtained as for the Cr<sub>LOAD</sub> group.

Group Cr<sub>LOAD+6</sub> consisted of six men (age 24 (3) years; BMI 25.6 (6.3) kg/m<sup>2</sup>) who ingested 5 g Cr plus 1 g glucose dissolved in a warm drink four times a day for five days. Blood samples for analysis were obtained before the start of supplementation and six weeks after the ingestion regimen had been completed, when muscle Cr stores would be expected to have returned to levels found before supplementation.<sup>8</sup>

Group P<sub>LOAD+6</sub> (a placebo group) consisted of six subjects (age 22 (2) years; BMI 21.7 (2.0) kg/m<sup>2</sup>; three men), who ingested 6 g glucose dissolved in a warm drink four times a day for five days. Blood samples for analysis were obtained as for the Cr<sub>LOAD+6</sub> group.

#### Effects of Cr loading and an eight week maintenance regimen

Group Cr<sub>MAINT</sub> consisted of seven women (age 26 (8) years; BMI 23.3 (1.9) kg/m<sup>2</sup>) who ingested a loading dose of 5 g Cr dissolved in a warm drink four times a day for five days, and who then maintained an intake of 3 g Cr in a warm drink, once a day for eight weeks. During this period, all subjects refrained from performing strenuous exercise. Blood samples for analysis were obtained before supplement ingestion on the first day of the loading dose

and on the day after the maintenance regimen had been completed.

Group Cr<sub>MAINT+EX</sub> consisted of nine women (age 27 (6) years; BMI 23.4 (3.2) kg/m<sup>2</sup>) who ingested a loading dose of 5 g Cr dissolved in a warm drink four times a day for five days, and who then maintained an intake of 3 g Cr in a warm drink, once a day for eight weeks. During the eight week maintenance period, subjects engaged in a resistance training programme. This exercise programme was used to create similar conditions to those of subjects who ingest Cr during periods of training to improve athletic performance, as anecdotal reports have been made of muscle cramps occurring during Cr supplementation and training.<sup>11</sup> The training programme involved three one hour supervised resistance training sessions each week. Blood samples for analysis were obtained as for the Cr<sub>MAINT</sub> group.

Group P<sub>MAINT+EX</sub> (a placebo group) consisted of six women (age 28 (5) years; BMI 24.5 (3.6) kg/m<sup>2</sup>) who ingested a "loading dose" of 5 g of a glucose polymer dissolved in a warm drink four times a day for five days, and who then maintained an intake of 3 g of glucose polymer in a warm drink, once a day for eight weeks. During the eight week supplementation period subjects engaged in a resistance training programme identical with that used by subjects in the Cr<sub>MAINT+EX</sub> group. Blood samples for analysis were obtained as for the Cr<sub>MAINT</sub> group.

#### Supplement formulations

Subjects in the Cr<sub>LOAD+6</sub>, P<sub>LOAD+6</sub>, Cr<sub>MAINT</sub>, Cr<sub>MAINT+EX</sub>, and P<sub>MAINT+EX</sub> groups were provided with supplements in a double blind manner. During the five day "loading dose" period, subjects in all groups were asked to ingest their supplement dose at four regularly spaced intervals evenly distributed throughout each day. During the eight week "maintenance dose", subjects ingested their daily supplement dose at the same time each day. All Cr was given in its monohydrate powder form (Experimental and Applied Science, Golden, Colorado, USA). The glucose polymer was provided as dextrose powder, and the carbohydrate drink as a commercially available solution (Lucozade; about 18.5% (w/v) glucose and simple sugars; SmithKline Beecham, Coleford, Gloucestershire, UK).

#### SAMPLING PROTOCOL

Subjects reported to the laboratory on the morning of the experiments after an overnight fast, having abstained from alcohol consumption and strenuous exercise during the previous

Table 2 Normal range<sup>16</sup> and mean (SD) values of haematological indices and indices of muscle damage and hepatic and renal function before (all groups), immediately after ( $Cr_{LOAD}$ ,  $P_{LOAD}$  groups), and six weeks after ( $Cr_{LOAD+6}$ ,  $P_{LOAD+6}$  groups) five days of creatine (Cr) or placebo (P) ingestion

Clinical index	Normal range	$Cr_{LOAD}$ group		$P_{LOAD}$ group		$Cr_{LOAD+6}$ group		$P_{LOAD+6}$ group	
		Pre	Post	Pre	Post	Pre	6 weeks	Pre	6 weeks
Sodium	135–145	141 (2)	141 (1)	141 (2)	142 (1)	139 (1)	141 (1)*	138 (1)	140 (2)
Potassium	3.5–5.0	4.0 (0.4)	3.9 (0.3)	4.0 (0.3)	4.3 (0.4)	4.0 (0.2)	4.0 (0.3)	4.1 (0.2)	4.0 (0.2)
Urea	2.5–7.0	4.4 (1.1)	3.8 (1.3)	4.9 (1.0)	3.5 (1.1)‡	4.1 (0.4)	5.3 (0.6)†	4.7 (0.7)	4.2 (0.7)
Creatinine	60–130	88 (15)	112 (30)	96 (14)	92 (18)	103 (10)	105 (10)	82 (8)	85 (12)
GGT	0–65	20 (5)	19 (4)	24 (7)	23 (8)	27 (7)	27 (9)	21 (7)	22 (6)
AP	30–110	67 (17)	72 (17)	71 (16)	72 (18)	72 (9)	72 (13)	64 (15)	61 (15)
ALT	5–40	25 (7)	24 (7)	22 (3)	25 (4)	27 (8)	30 (7)	19 (3)	21 (3)
Albumin	35–50	44 (3)	43 (2)	44 (2)	44 (2)	47 (4)	45 (1)	47 (2)	45 (2)‡
Bilirubin	5–17	14 (5)	12 (6)	16 (3)	12 (3)†	12 (2)	10 (2)	12 (4)	10 (3)
CK	Up to 200	Not measured		Not measured		152 (85)	127 (34)	92 (42)	123 (108)
Hb	11.5–18.0	14.0 (0.8)	14.0 (0.9)	14.6 (0.3)	14.4 (0.6)	14.9 (0.8)	14.7 (0.6)	13.9 (1.3)	13.4 (1.1)
WBC	4.0–11.0	5.0 (1.5)	5.5 (0.9)	5.7 (1.4)	7.0 (1.4)	6.2 (1.0)	6.7 (1.3)	5.3 (1.4)	5.3 (1.2)
Platelets	150–400	197 (47)	212 (39)	233 (63)	243 (60)	263 (48)	236 (40)	223 (62)	214 (43)

Measurement units for haematological indices and indices of muscle damage and hepatic and renal function; sodium (mmol/l), potassium (mmol/l), urea (mmol/l), creatinine ( $\mu$ mol/l),  $\gamma$ -glutamyl transferase (GGT; U/l), alkaline phosphatase (AP; U/l), alanine aminotransferase (ALT; U/l), albumin (g/l), total bilirubin ( $\mu$ mol/l), creatine kinase (CK; U/l), haemoglobin (Hb; g/100 ml), white blood cells (WBC;  $\times 10^9/l$ ), platelets ( $\times 10^9/l$ ).

\* $p < 0.05$ , † $p < 0.01$ , and ‡ $p < 0.001$  indicate significant differences between the values before (Pre) and after (Post) supplementation within each group.

48 hours. Height and body mass (in underwear) were recorded. Blood samples were taken at rest by venepuncture (using the Vacutainer system, from an antecubital vein of the left or right arm) after subjects had been seated for at least five minutes. Samples for clinical chemistry analyses were dispensed into plain tubes (containing no anticoagulant), and samples for haematological analysis were dispensed into tubes containing EDTA. Samples were subsequently analysed for indices of renal function (serum sodium, potassium, urea, and creatinine concentrations), hepatic function (serum  $\gamma$ -glutamyl transferase, alkaline phosphatase, and alanine aminotransferase activity, and albumin and total bilirubin concentrations), and indices of haematological function (haemoglobin concentration was measured and white blood cells and platelets counted). In addition, an index of muscle damage (serum creatine kinase activity) was measured in the groups assessed six weeks after acute supplementation and after the more chronic maintenance regimen. All analyses were by routine methods in use at the University Hospital, Queen's Medical Centre, Nottingham.

#### STATISTICAL ANALYSIS

Student's *t* test was used to compare values determined before and after supplementation in each of the groups (paired), and to compare the changes between corresponding Cr and placebo groups (unpaired), using a commercially available computer software package (Microsoft Excel). Statistical significance was declared at  $p < 0.05$ .

#### Results

All subjects reported adherence to the experimental protocol and complete ingestion of the supplements. None reported any adverse effects throughout the period of the study.

#### EFFECTS OF A Cr LOADING DOSE REGIMEN

Group mean data of all indices measured were within the normal range before, the day after, and six weeks after the loading regimen (table 2). On the day after Cr loading, there was no significant difference in any of the indices measured before Cr loading; however, moderate decreases were observed in serum urea and bilirubin concentrations of the placebo group. Although there were no differences in absolute concentrations, there was a significant between

Table 3 Normal range<sup>16</sup> and mean (SD) values of haematological indices and indices of muscle damage and hepatic and renal function before and immediately after five days of creatine or placebo ingestion followed by an eight week Cr or placebo maintenance regimen in the presence and absence of exercise training

Clinical index	Normal range	$Cr_{MAINT+EX}$ group		$Cr_{MAINT}$ group		$P_{MAINT+EX}$ group	
		Pre	Post	Pre	Post	Pre	Post
Sodium	135–145	140 (2)	139 (2)	140 (2)	140 (1)	141 (2)	140 (1)
Potassium	3.5–5.0	3.9 (0.2)	4.1 (0.2)†	3.9 (0.2)	4.1 (0.3)†	3.9 (0.3)	4.2 (0.2)
Urea	2.5–7.0	3.6 (0.7)	3.6 (0.8)	4.2 (0.7)	3.8 (0.4)	4.3 (0.6)	3.6 (0.8)†
Creatinine	54–117	69 (6)	86 (15)*	68 (4)	95 (17)*	78 (9)	72 (5)
GGT	0–40	19 (5)	21 (4)	19 (5)	20 (4)	41 (54)	31 (28)
AP	30–110	52 (6)	60 (12)†	53 (8)	55 (9)	67 (18)	64 (11)
ALT	5–40	27 (4)	22 (3)	26 (4)	21 (4)†	30 (5)	28 (9)
Albumin	35–50	40 (2)	43 (2)†	40 (3)	44 (3)†	41 (3)	43 (2)
Bilirubin	5–17	10 (4)	10 (2)	9 (2)	10 (2)	12 (6)	12 (2)
CK	up to 200	142 (149)	142 (48)	91 (59)	91 (34)	186 (194)	198 (145)
Hb	11.5–16.5	12.2 (1.0)	12.2 (0.8)	12.3 (1.1)	12.8 (0.8)	13.3 (1.0)	13.2 (1.1)
WBC	4.0–11.0	5.9 (0.6)	6.2 (1.2)	6.5 (1.3)	6.8 (1.5)	6.7 (1.4)	6.0 (0.6)
Platelets	150–400	244 (59)	249 (58)	268 (21)	292 (59)	274 (43)	267 (70)

Measurement units for haematological indices and indices of muscle damage and hepatic and renal function; sodium (mmol/l), potassium (mmol/l), urea (mmol/l), creatinine ( $\mu$ mol/l),  $\gamma$ -glutamyl transferase (GGT; U/l), alkaline phosphatase (AP; U/l), alanine aminotransferase (ALT; U/l), albumin (g/l), total bilirubin ( $\mu$ mol/l), creatine kinase (CK; U/l), haemoglobin (Hb; g/100 ml), white blood cells (WBC;  $\times 10^9/l$ ), platelets ( $\times 10^9/l$ ).

\* $p < 0.05$  and † $p < 0.01$  indicate significant differences between values before (Pre) and after (Post) supplementation within each group.

group difference in the change in serum creatinine concentration over time ( $Cr_{LOAD}$ , 24 (10)  $\mu\text{mol/l}$ ;  $P_{LOAD}$ , -3 (2)  $\mu\text{mol/l}$ ;  $p < 0.05$ ). This difference was not evident six weeks after the completion of the loading dose ( $Cr_{LOAD+6}$ , 2 (2)  $\mu\text{mol/l}$ ;  $P_{LOAD+6}$ , 3 (2)  $\mu\text{mol/l}$ ;  $p > 0.05$ ). Serum sodium and urea concentrations had increased in the  $Cr_{LOAD+6}$  group six weeks after completion of Cr loading (table 2). The change in serum urea concentration with time was significantly different in the  $Cr_{LOAD+6}$  group compared with its placebo group ( $Cr_{LOAD+6}$ , 1.2 (0.3)  $\text{mmol/l}$ ;  $P_{LOAD+6}$ , -0.4 (0.2)  $\text{mmol/l}$ ;  $p < 0.001$ ). A moderate decrease in serum albumin concentration was observed in the  $P_{LOAD+6}$  group.

#### EFFECTS OF A CR MAINTENANCE DOSE REGIMEN

Group mean data of all indices measured were within the normal range before the Cr loading regimen and on the day after the maintenance regimen was completed (table 3). Small to moderate increases in serum potassium, creatinine, and albumin were observed in both groups receiving Cr. In addition, there was a small decrease in alanine aminotransferase concentration in the  $Cr_{MAINT}$  group and an increase in alkaline phosphatase in the  $Cr_{MAINT+EX}$  group. There was a significant decrease in serum urea concentration in the  $P_{MAINT+EX}$  group. The changes in serum creatinine concentration over time in the groups receiving Cr were significantly different from those in the placebo group ( $Cr_{MAINT}$ , 26 (6)  $\mu\text{mol/l}$ ;  $Cr_{MAINT+EX}$ , 17 (4)  $\mu\text{mol/l}$ ;  $P_{MAINT+EX}$ , -6 (3)  $\mu\text{mol/l}$ ;  $p < 0.001$ ,  $p < 0.01$  respectively).

#### Discussion

We believe that this is the first detailed information to be reported on the effects of short term (20 g/day for five days) and more chronic (3 g/day for 56 days) Cr supplementation on a range of some haematological indices and indices of hepatic, muscle, and renal function, in young healthy adults. Information on some of these indices in older adults (older than 51) during eight weeks of Cr supplementation has been published in abstract form,<sup>17, 18</sup> while more recent work has reported some clinical chemistry indices in male athletes ingesting Cr for 28 days,<sup>19</sup> and renal responses in healthy men after short term supplementation.<sup>20</sup> In none of these reports were adverse responses reported. Data from blood samples taken before supplementation, on the day after, and six weeks after an established Cr loading dose regimen, and after a subsequent eight week maintenance dose of 3 g/day have been examined in this study. Mean concentrations of all indices were well within the normal range<sup>16</sup> at all times.

Creatinine has been established as the sole end product of Cr degradation, being formed non-enzymatically in an irreversible reaction.<sup>21, 22</sup> As skeletal muscle is the major store of the body Cr pool,<sup>10</sup> it is therefore the main site of creatinine production. In normal healthy people, plasma creatinine concentration is dependent on total muscle mass,<sup>23</sup> thus daily renal creatinine excretion is relatively constant in a given individual, but can vary

between individuals.<sup>24</sup> In the present study, serum creatinine concentration on the day after Cr loading was within the normal range and was not significantly higher than that before supplementation. However, the relative change in concentration over time was significantly greater in the  $Cr_{LOAD}$  group than in the placebo group. This difference in the change in serum creatinine concentration merely reflects an increased rate of muscle creatinine formation as a result of the dietary induced increase in muscle Cr stores, and has been reported previously, together with a parallel increase in urinary creatinine excretion.<sup>8</sup> Six weeks after discontinuation of Cr loading, there was no indication of an elevated serum creatinine concentration. Muscle TCr will have returned close to the level found before supplementation by this time,<sup>8</sup> as will have renal creatinine excretion. Maintaining elevated muscle Cr concentration by ingesting 3 g Cr a day after Cr loading increased serum creatinine concentration above that seen before supplementation. However, these concentrations were again within the normal range and, as outlined above, were probably attributable to the increase in muscle Cr concentration.

We suggest that the increase in serum urea six weeks after the Cr loading regimen is of little clinical significance and unlikely to be a direct result of Cr supplementation. This contention is supported by the lack of any difference in serum urea concentration on the day after a Cr loading regimen and after more chronic supplementation with and without training.

Serum sodium concentration was increased six weeks after Cr loading. However, the absence of any similar change on the day after the end of supplementation suggests that this was unlikely to be due to supplementation, and the magnitude of the change would be expected to be of little clinical significance. Similarly, the increase in serum potassium concentration after chronic Cr supplementation was small and unlikely to be of clinical significance.

All hepatic function indices were within the normal limits before and after creatine loading. The changes observed in serum alkaline phosphatase ( $Cr_{MAINT+EX}$ ) and alanine aminotransferase ( $Cr_{MAINT}$ ) activity and albumin ( $P_{LOAD+6}$ ,  $Cr_{MAINT+EX}$ ,  $Cr_{MAINT}$ ) and bilirubin ( $P_{LOAD}$ ) concentrations with time were all marginal and occurred in both directions. We suggest that these changes are unlikely to be of clinical significance and probably unrelated to the experimental protocol.

The haematological indices measured were unchanged by the supplementation protocols. Serum creatine kinase activity, an accepted marker of muscle damage, was unchanged six weeks after acute Cr supplementation, nor was it changed after more chronic supplementation in the presence and absence of resistance training. This latter finding is of interest, as anecdotal comments have linked Cr supplementation to the development of muscle cramps and muscle-tendon injury during or after exercise.<sup>11</sup>

In the present study, there were no reports of muscle cramping or injury.

In conclusion, no clinically significant changes in the haematological indices measured, nor in indices of muscle damage or hepatic and renal function, were observed after acute Cr loading or eight weeks of lower dose maintenance ingestion. The present data therefore suggest that there is no obvious risk to health of ingesting creatine supplements. Indeed, the 2–3 g a day maintenance dose of Cr currently advocated to maintain muscle Cr concentration after Cr loading<sup>8</sup> is similar to the amount of Cr used daily by the body and could be partly achieved from meat and fish ingestion.

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### Take home message

Recently there have been some concerns that creatine supplementation may have adverse effects on health. This paper investigated the effect of acute and more prolonged creatine supplementation on some haematological indices and indices of hepatic, muscle, and renal function. The data presented provide evidence that there are no adverse effects of acute or more chronic creatine supplementation on any of the indices measured and suggest that there is no obvious risk to health of ingesting creatine supplements at the recommended doses.