CHAPTER 14

SAFETY OF CREATINE SUPPLEMENTATION

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Abstract: The literature on creatine supplementation supporting its efficacy has grown rapidly and has included studies in both healthy volunteers and patient populations. However, the first rule in the development of therapeutic agents is safety. Creatine is well-tolerated in most individuals in short-term studies. However, isolated reports suggest creatine may be associated with various side effects affecting several organ systems including skeletal muscle, the kidney and the gastrointestinal tract. The majority of clinical studies fail to find an increased incidence of side effects with creatine supplementation. To date, studies have not found clinically significant deviations from normal values in renal, hepatic, cardiac or muscle function. Few data are available on the long-term consequences of creatine supplementation

1. INTRODUCTION

Creatine is an endogenous molecule whose primary role is to act as an 'energy buffer'. Supraphysiologic doses of creatine have been shown to increase muscle stores of creatine and phosphocreatine, enhance muscle strength, reduce fatigue during exercise and improve exercise performance [see Branch (2003) for a meta-analysis]. Furthermore, there is a growing body of literature on pre-clinical and clinical evidence that creatine has a positive therapeutic outcome in various neurological or muscular diseases.

While creatine is well tolerated by most individuals in short-term studies, anecdotal reports and a small number of case-reports suggest that creatine may be associated with various side effects ranging from muscle cramping and gastrointestinal discomfort to renal dysfunction. Safety, whether it is a drug, food or supplement, does not imply the product is harmless, but that the therapeutic (or nutritional) benefits outweigh the risks of side effects for the intended population. As an example, the cholesterol-lowering agent Baycol (cerivastatin) was as effective

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as other statin medications in lowering cholesterol; however, cerivastatin caused severe muscle damage prompting its removal from the market in August 2001 (Charatan, 2001). Adverse events such as severe muscle damage are unacceptable for drug classes for non-life threatening diseases. This risk to benefit ratio helps classify compounds into categories of high therapeutic index (e.g., most over-the-counter medications) or low therapeutic index (e.g., medications that are routinely monitored such as warfarin or lithium). Creatine would be clinically useful if the desired therapeutic effects (e.g., increased muscle strength, reduced fatigue) outweighed the undesired pharmacologic/toxicologic effects (e.g., muscle cramping).

The purpose of this chapter is to summarize the evidence related to the safety of creatine supplements. Although there are safety data available from studies of creatine supplementation in animals, experimental data from animal models may not be directly applicable to the effects of creatine in humans. For instance, Green *et al.* (1996b) reported no increase in muscle creatine content in rats ingesting creatine in amounts equivalent to the dosages used in human studies. Additionally, creatine uptake is significantly enhanced in the presence of insulin in human skeletal muscle (Green *et al.*, 1996a,b; Preen *et al.*, 2003; Robinson *et al.*, 2000), but to a much lesser extent in rat skeletal muscle (Koszalka *et al.*, 1972). Most recently, species differences (rats vs. mice) in the response to creatine supplementation have been reported (Kreider, 2003; Tarnopolsky *et al.*, 2003). With that in mind, this chapter focuses on data regarding the safety of creatine supplementation from clinical trials and case studies.

2. SAFETY FINDINGS

2.1. Muscle Dysfunction

Creatine supplementation has been associated with increased muscle dysfunction (i.e. cramps, muscle strains, etc.) in the popular media. Increased muscle creatine content subsequent to creatine supplementation is associated with increased total body water (Powers *et al.*, 2003) and increased compartment pressure (Hile *et al.*, 2006). This resulted in the speculation that creatine supplementation could cause muscle dysfunction. In theory, increased muscle phosphocreatine levels resulting from creatine supplementation may reduce muscle dysfunction, as it is known that exogenous phosphocreatine reduces muscle damage in cardiac tissue as evidenced by decreased efflux of cardiac muscle proteins into the blood (Saks *et al.*, 1996; Saks and Strumia, 1993). In fact, phosphocreatine is used as a cardio-protective agent during heart surgery and to reduce infarct size after myocardial infarction (Saks *et al.*, 1996; Saks and Strumia, 1993). The effects of creatine supplementation on mild and severe indices of skeletal muscle dysfunction have been studied in cross-sectional studies, clinical trials, and case studies, as outlined below.

2.1.1. Cramping

Muscle cramping in creatine users has been reported by some groups. However, placebo or non-creatine user groups were not included for comparison, so that the relationship between creatine and muscle cramps cannot be determined from these studies (Greenwood *et al.*, 2000; Juhn *et al.*, 1999). A series of open label studies by Greenwood *et al.* (2003b,c) and one retrospective study (Schilling *et al.*, 2001) reported either similar instances of muscle dysfunction (i.e. cramping, muscle tightness, strains, injuries, etc.) between creatine and non-creatine users or fewer instances of muscle dysfunction in creatine users (Greenwood *et al.*, 2003a). Recently, Watson *et al.* (2006) reported no increase in cramping in creatine-supplemented subjects following dehydration and an 80 minute exercise heat tolerance test (33.5°C, 41% relative humidity). In this study, plasma sodium and potassium, and the dehydration levels following exercise, were unaffected by creatine ingestion, so it is not surprising that there was no increase in cramping (Watson *et al.*, 2006). Currently, there appears to be no empirical evidence linking creatine to muscle cramps.

2.1.2. Muscle damage

Reportedly, creatine ingestion has no effect on indices of muscle damage (e.g. blood creatine kinase or lactate dehydrogenase under resting conditions) (Kreider *et al.*, 2003; Mihic *et al.*, 2000; Robinson *et al.*, 2000; Schilling *et al.*, 2001). Three clinical studies have examined the interaction between creatine supplementation, extreme exercise, and muscle damage (Rawson *et al.*, 2001, 2007; Santos *et al.*, 2004). Rawson *et al.* (2001, 2007) found no effect of creatine on markers of muscle damage (decreased strength, decreased range of motion, increased muscle soreness, and increased serum creatine kinase and lactate dehydrogenase activity) following 50 high-force eccentric contractions of the elbow flexors or a high-repetition squat exercise challenge. These data were supported in a study by Warren *et al.* (2000) using an animal model. Santos *et al.*, (2004) reported that creatine supplementation attenuated the increase in plasma creatine kinase (by 19%), prostaglandin E_2 (by 61%), and tumor necrosis factor-α (by 34%) and eliminated the increase in plasma lactate dehydrogenase following a 30 km run, indicating less muscle damage. Collectively, clinical studies of the interactions between creatine supplementation and extreme exercise stress indicate that creatine supplementation does not exacerbate muscle damage (Rawson *et al.*, 2001, 2007) and might protect muscle from damage during certain types of stressful exercise (Santos *et al.*, 2004). It is important to note that serious adverse events associated with severe muscle damage (i.e. rhabdomyolysis), which may occur infrequently (1 in 10,000 exposures), are difficult to detect in the small clinical trials typically conducted on creatine supplementation ($n < 50$). The effects of creatine supplementation on indirect markers of muscle damage from double-blind placebo-controlled trials are described in Table 1.

Table 1. Effects of creatine supplementation on indices of muscle damage in double-blind placebo-controlled trials .

Outcome Variable	Exercise Challenge	Reference
Ø in resting plasma CK	-	Mihic *et al.*, 2000
Ø in resting serum CK	-	Robinson *et al.*, 2000
Ø in post-exercise serum CK and LDH, ROM, strength, DOMS	50 maximal eccentric contractions of the elbow flexors	Rawson *et al.*, 2001
Ø in post-exercise serum CK and LDH, ROM, strength, DOMS	5 sets of 15-20 squats with 50% of 1-RM	Rawson *et al.*, 2007
↓ in post-exercise plasma CK (19%), PGE_2 (61%), TNF-α (34%) and LDH (100%)	30 km run	Santos *et al.*, 2004

Note: Ø indicates no effect of creatine; ↓ indicates a decrease following creatine ingestion; ↑ indicates an increase following creatine ingestion. CK = creatine kinase, LDH = lactate dehydrogenase, ROM = range of motion, DOMS = delayed onset muscle soreness, PGE_2 = prostaglandin E_2, TNF-α = tumor necrosis factor α.

2.1.3. Rhabdomyolysis

Despite the intense media scrutiny on creatine supplementation, few cases of severe rhabdomyolysis in creatine users have been reported in the literature (Kuklo *et al.*, 2000; Robinson, 2000; Sandhu *et al.*, 2002; Sheth *et al.*, 2006). Robinson (2000) reported compartment syndrome and severe rhabdomyolysis in a patient who had been taking five times the recommended dosage of creatine (25 g/day) for one year and had performed three hours of lower extremity exercise the day before. Thus, it is unclear if the rhabdomyolysis was precipitated by the high-dose creatine supplementation, was a result of stressful unaccustomed resistance exercise, or a combination of the two. Similarly, rhabdomyolysis and compartment syndrome have been reported following stressful exercise in patients who had been ingesting creatine in combination with other supplements (e.g. ephedrine, natural diuretics) (Kuklo *et al.*, 2000; Sandhu *et al.*, 2002). Sheth *et al.* (2006) described a case of rhabdomyolysis in a creatine user in the days following arthroscopic knee surgery. It is uncommon, but post-operative rhabdomyolysis has been reported. Overall, it is unclear what role creatine supplementation played in these cases of severe rhabdomyolysis. It may be that in those who are predisposed to exercise-induced rhabdomyolysis, the combination of creatine supplementation and stressful unaccustomed exercise worsens symptoms compared to exercise alone, although this is speculative.

2.2. Dehydration

Creatine is often incorrectly associated with dehydration. In fact, creatine supplementation increases total body water (Powers *et al.*, 2003) and is more correctly

referred to as a hyper-hydrating agent. Powers *et al.* (2003) used deuterium oxide and sodium bromide dilution analyses to demonstrate a 1.4 liter and 2.0 liter increase in total body water following 7 and 21 days of creatine supplementation, respectively. It has been proposed that creatine supplementation may bind water inside the muscle cell, making it unavailable for heat loss through the evaporation of sweat. However, Powers *et al.* (2003) reported that fluid distribution was unaffected by creatine supplementation (i.e. the intra- and extracellular water ratios were unaltered).

Several researchers have investigated thermoregulatory responses and exercise performance (Kern *et al.*, 2001; Kilduff *et al.*, 2004; Mendel *et al.*, 2005; Vogel *et al.*, 2000; Volek *et al.*, 2001; Watson *et al.*, 2006) in creatine-supplemented individuals following heat stress and/or hypohydration (Table 2). Collectively, these studies demonstrate that creatine-induced hyper-hydration does not impair thermoregulatory or metabolic responses to prolonged exercise in the heat. In fact, creatine may attenuate thermoregulatory responses and prevent heat related injuries and performance decrements (Kilduff *et al.*, 2004). For instance, Kilduff *et al.* (2004) reported decreased heart rate, perceived leg fatigue, rectal and body temperature, and sweat rate in creatine-supplemented individuals cycling to exhaustion in the heat (see Table 2). In the most comprehensive study to date, Watson *et al.* (2006) demonstrated that creatine supplementation does not adversely affect a number of variables spanning thermoregulatory, metabolic, and perceived responses to exercise in the heat in hypohydrated individuals (see Table 2). Although it has been theorized that increased total body water associated with creatine ingestion may cause thermoregulatory disturbances when exercise is combined with heat stress, the data do not support this.

2.3. Renal Dysfunction

Although the kidney has many physiologic functions it is most noted for its excretory function. The kidneys are responsible for predominantly removing small, hydrophilic molecules from the blood. Creatine and its major metabolite, creatinine, are both cleared from the blood by the kidney. Creatinine is an important clinical marker for renal function; more specifically, creatinine clearance is an indicator of glomerular filtration rate (GFR). Creatinine clearance is most frequently calculated from a single serum creatinine sample and the subsequent use of the Cockcroft-Gault equation, although other equations are available. The use of serum creatinine as a marker for renal function requires several assumptions, including: 1) the daily anabolic production of creatine is constant and 2) the conversion of creatine to creatinine is constant, and non-constant sources do not exist. During creatine supplementation, the first assumption is violated because supraphysiologic doses consumed far exceed daily endogenous production (daily liver production $\sim$1 g/d, typical dosing 3–20 g/day). This in turn reduces endogenous creatine synthesis (Walker and Hannan, 1976). The second assumption of constant conversion is not violated however, as creatine stores increase with creatine dosing, so does serum creatinine. This is expected assuming the rate of degradation into creatinine is

Table 2. Effects of creatine supplementation on thermoregulatory responses and exercise performance in heat-stressed and hypohydrated individuals .

Effect of Creatine on Outcome Variables	Exercise/Environmental stress	Reference
Ø resting & post-exercise HR; Ø resting & post-exercise BP; Ø exercise T_{rect}; Ø exercise sweat rate; Ø post-exercise body mass; Ø post-exercise hemoglobin, hematocrit, & plasma volume; Ø post-exercise cortisol, aldosterone, renin, vasopressin, angiotensin I & II, & atrial peptide; Ø post-exercise urine volume, sodium, potassium, creatinine, and specific gravity; Ø reported muscle dysfunction; Ø RPE; Ø exercise performance	30 min cycling at 60 to 70% $VO_{2,peak}$ followed by three 10 s maximal sprints in an environmental chamber set at 37°C and 80% relative humidity	Volek *et al.*, 2001
Ø post-exercise body mass; Ø plasma volume; Ø exercise performance; Ø reported muscle dysfunction	Exercise and rest conducted in an environmental chamber set at 32°C and 50% relative humidity; 20 min rest in environmental chamber, five 5 s maximal cycling sprints, 75 min intermittent cycling (to reduce body mass 3 to 5%), 20 min rest in environmental chamber, five 5 s maximal cycling sprints, 75 min intermittent cycling, 20 min in environmental chamber, five 5 s maximal cycling sprints	Vogel *et al.*, 2000
Ø resting hematocrit; Ø resting & exercise HR; ↓ exercise T_{rect}	60 min cycling at 60% $VO_{2,max}$ in an environmental chamber set at 37°C and 25% relative humidity	Kern *et al.*, 2001
Ø time to exhaustion; ↓ exercise HR; ↓ RPE; ↓ exercise T_{rect} & T_{body}; Ø T_{skin}; ↓ exercise sweat rate; Ø sweat loss; Ø exercise metabolic rate, VO_2, VCO_2, V_E, RER; Ø exercise plasma volume	Cycling to exhaustion at 63% $VO_{2,max}$ in an environmental chamber set at 30°C and 70% relative humidity	Kilduff *et al.*, 2004
Ø exercise T_{rect}, T_{skin}, T_{body}; Ø reported thermal sensation	40 min cycling at 55% $VO_{2,max}$ in an environmental chamber set at 39°C and 26% relative humidity	Mendel *et al.*, 2005
Ø post-dehydration and post-exercise body mass; Ø exercise sweat loss; Ø exercise T_{rect}, T_{skin}; Ø exercise VO_2, HR, BP, MAP, lactate; Ø perceived environmental symptoms; Ø exercise plasma osmolality, volume, lactate, protein, sodium, potassium; ↑ post-dehydration plasma osmolality; ↑ exercise plasma glucose; ↓ post-exercise urine osmolality; ↑ resting, pre-exercise, and post-exercise urine specific gravity; Ø resting urine osmolality, specific gravity, color, volume	120 min cycling/treadmill walking in an environmental chamber set to 33.5°C and 41% relative humidity (to reduce body mass 2%), 80 min of alternatively running, walking, and standing	Watson *et al.*, 2006

Note: Ø indicates no effect of creatine; ↓ indicates a decrease following creatine ingestion; ↑ indicates an increase following creatine ingestion. HR = heart rate, BP = blood pressure, T_{rect} = rectal temperature, T_{body} = body temperature, T_{skin} = skin temperature, RPE = rating of perceived exertion, VO_2 = oxygen consumption, VCO_2 = carbon dioxide production, V_E= ventilation, RER = respiratory exchange ratio, MAP = mean arterial pressure.

concentration-dependent (i.e., a first-order process). This increase in stores can make the body appear to have a larger muscle mass than accounted for in the ideal body weight parameter of the Cockroft-Gault equation.

Clinical studies examining changes in serum creatinine with supplementation have found serum creatinine either does not change or increases but remains in the normal range ($\sim$ 0.5 to 1.5 mg/dL for adults) (Table 3). Some concern has been raised by this increase because it is assumed a rise in serum creatinine indicates reduced kidney function. However, studies using both serum and urine creatinine to estimate renal function in healthy individuals (Kreider *et al.*, 2003; Mihic *et al.*, 2000; Poortmans and Francaux, 1999) and patients (Groeneveld *et al.*, 2005; Louis *et al.*, 2003; Tarnopolsky *et al.*, 2004; Tarnopolsky and Raha, 2005) have found no change in kidney function. Recently, it was reported that 16 months of creatine supplementation had no effect on plasma urea and micro-albuminuria (indirect markers of renal dysfunction) in 175 patients with amyotrophic lateral sclerosis (ALS) (Groeneveld *et al.*, 2005). No changes in renal function have been noted in dystrophic patients as well (Louis *et al.*, 2003).

Since Harris *et al.* (1992) first demonstrated that muscle creatine levels could be increased with oral creatine supplementation, there have been over 200 clinical studies (through 2006) examining the impact of creatine supplementation. Of the hundreds of clinical studies examining the effects of creatine supplementation, and the thousands of exposures to creatine through these studies and through use by the general population, we are aware of three case studies where individuals developed renal dysfunction during creatine ingestion (Koshy *et al.*, 1999; Pritchard and Kalra, 1998; Revai *et al.*, 2003).

In the first case study, a 20-year old male with nausea, vomiting and bilateral flank pain was consuming 20 g/d creatine (5 g four times a day) for four weeks prior to hospital admittance (Koshy *et al.*, 1999). His serum creatinine was 1.4 mg/dL and urine analysis was positive for protein and red blood cells. Renal biopsy revealed acute focal interstitial nephritis and focal tubular injury. The patient did recover during his hospital admission. Most cases of interstitial nephritis are hypersensitivity reactions to medications such as non-steroidal anti-inflammatory drugs or antibiotics; in addition, obstruction of the tubules can cause this pathology as well. There was no evidence of inflammation hypersensitivity to creatine or renal obstruction as possible causes of the nephritis in this patient. It is possible that the dysfunction was caused by changes in osmotic gradient as seen with compounds such as mannitol.

The second case study involved a 25-year old male with focal segmental glomerulosclerosis with relapsing steroid responsive nephrotic syndrome (Pritchard and Kalra, 1998); he was taking cyclosporine for the previous 5 years to minimize nephrotic episodes and drug concentrations were within the therapeutic range. The patient had a history of normal renal function but the patient's creatinine clearance started to decline over time. The patient admitted to taking 15 g/d creatine (5 g three times a day) for 1 week followed by 2 g/d maintenance therapy. One month after stopping the creatine supplement, creatinine clearance returned to normal. A later

Table 3. Clinical studies examining serum creatinine (or creatinine clearance) responses during creatine supplementation. Serum creatinine is used as a clinical marker of renal function (normal limits: 0.5 to 1.5 mg/dL). The table summarizes data from 21 studies with creatine supplementation regimes ranging from 2 to 30 g/d for 1 d to 5.6 yrs. "load" = loading dose; "maint" = maintenance dose .

Study Finding	Number of Studies	Dose Amount	Duration Range	References
Studies finding no change in serum creatinine	12	15.75 g/d (load) 5 g/d (maint)	5 d up to 21 months	Kreider *et al.*, 2003
		20 g/d	5 d	Robinson *et al.*, 2000 #
		20 g/d	5 d	Poortmans *et al.*, 1997
		3 to 30 g/d	10 mo to 5 yr	Poortmans and Francaux, 1999
		10 g/d	Up to 310 d	Groeneveld *et al.*, 2005
		2 g	1 d	Harris *et al.*, 1992
		21 g/d	10 d	Poortmans *et al.*, 2005
		2.5 g	1 d	Harris *et al.*, 2004
		20 g/d (load) 5 g/d (maint)	5 d 3 yr	Schroder *et al.*, 2005
		20 g/d	2 d	Mendes *et al.*, 2004
		3 g/d	3 mo	Louis *et al.*, 2003
		20 g/d (load) 5 g/d (maint)	5 d 3-4 d	Parise *et al.*, 2001
Studies finding an increase in serum creatinine but within normal limits	8	20 g/d (load) 3 g/d (maint)	5 d 8 wk	Robinson *et al.*, 2000 #
		20 g	1 d	Schedel *et al.*, 1999
		20 g/d	5 d	Kamber *et al.*, 1999
		20 g/d	5 d	Mihic *et al.*, 2000
		5 g/d	16 wk	Tarnopolsky *et al.*, 2004
		0.3 g/kg/d	7 d	Volek *et al.*, 2001
		10 g/d	10 wk	Tarnopolsky and Raha, 2005
		13.7 ± 10.0 g/d (load) 9.7 ± 5.7 g/d (maint)	0.8 to 4 yr	Schilling *et al.*, 2001
Studies finding an increase in serum creatinine above normal limits	2	5 to 20 g/d	0.25 to 5.6 yr	Mayhew *et al.*, 2002*
		20 g/d	5 d	Skare *et al.*, 2001

*However, serum creatinine was not different from control group.
There was no difference in serum creatinine after the initial 20 g/d loading phase, but serum creatinine did increase after the 8-week maintenance phase.

study found that cyclosporine does impact the kinetics of creatine transport, and the interaction of cyclosporine with creatine might explain the renal dysfunction (Tran *et al.*, 2000).

In the third case study (full publication is available in Hungarian), the patient was "continuously" taking a "large quantity" of the anabolic-androgenic steroid methandion and 200 grams of creatine per day and subsequently developed diffuse membranoproliferative glomerulonephritis type I (Revai *et al.*, 2003). In all three case studies, the patients either had previous renal disease (i.e., glomerulosclerosis with relapsing nephrotic syndrome) or ingested 4 to 100 times the recommended daily amount of creatine for extended periods of time with or without other anabolic agents. Conversely, several human clinical trials have been published demonstrating that creatine has no adverse effects on renal health (see Table 3) in individuals ingesting creatine supplements for up to five years.

2.4. Other

Although the effects of creatine supplementation on muscle function, thermoregulation, and renal function comprise the bulk of the available safety data, several other areas have been studied. These include the effects of creatine on gastrointestinal, hepatic, and cardiovascular health, production of undesirable metabolites subsequent to creatine supplementation, and product impurities.

2.4.1. Gastrointestinal, hepatic, and cardiovascular health

Anecdotal reports of gastrointestinal distress and diarrhea have been associated with creatine ingestion. Potentially, this could result from the ability of creatine to draw water into the intestine in a similar manner to how creatine draws water into the muscle. This could be prevented by ingestion of smaller quantities of creatine per serving, ingesting creatine in a liquid dosage form compared to a solid dosage form, and avoiding fruit juice consumption which may further increase the discomfort because of the osmotic potential of fructose.

To date, there are no reports of hepatic or cardiovascular dysfunction from clinical trials of creatine supplementation. Several studies have shown that creatine does not impact blood-based liver function tests (Kamber *et al.*, 1999; Kreider, 2003; Mayhew *et al.*, 2002; Robinson *et al.*, 2000). Further, systolic and diastolic blood pressure appear to be unaffected by creatine supplementation in young (Mihic *et al.*, 2000) and older subjects (Rawson *et al.*, unpublished observations). Earnest *et al.* (1996) reported decreased total cholesterol (6%), triglycerides (26%), and very low density lipoprotein in hypercholesterolemic men and women (32 to 70 yrs) supplemented with creatine for 56 days. However, Volek *et al.* (2000) found no additional effect of creatine on blood lipids when combined with resistance exercise training.

There is one case study related to creatine ingestion and cardiac dysfunction. A 30 year-old vegetarian male developed diarrhea and cramps after one month of creatine supplementation, and subsequently changed to a different creatine supplement and developed palpitations and dyspnea (Kammer, 2005). The patient underwent chemical conversion and cardiac catheterization to correct the arrhythmia. It is unknown what role creatine played in this case.

2.4.2. Metabolites

There is some concern that creatine may form formaldehyde through a minor metabolic pathway, and in this regard, it was recently hypothesized that creatine supplementation could be cytotoxic (Yu and Deng, 2000). Creatine can be converted to formaldehyde and hydrogen peroxide, and formaldehyde has the potential to cross-link proteins and DNA leading to cytotoxicity. Yu and Deng (2000) did find an increase in urine formaldehyde after creatine administration; however, they did not measure markers of protein or DNA cross-linking or measures of oxidative stress. Another study examined urinary methylamine, formaldehyde and formate with creatine supplementation (Poortmans *et al.*, 2005). These investigators found increases in both methylamine and formaldehyde when subjects ingested 21 g/d for 14 d. The increase in methylamine was still below the upper-limit of normal but for formaldehyde, no safety range has been established.

2.4.3. Impurities

In the United States, creatine is not regulated for its processing and impurities, so as with other dietary supplements, there is some concern that contaminants may lead to adverse effects with creatine use. Benzi (2000) theorized that because creatine is produced from the reaction of sarcosine and cyanamide, several possible contaminants such as creatinine, dicyandiamide, dihydrotriazines, and ions such as arsenic could be produced. Although many creatine manufacturers provide a certificate of analysis with their products that addresses the issue of impurities, these findings have not been confirmed in many independent analyses. At least two studies examined creatine product quality with respect to percent labeled claim (Dash and Sawhney, 2002; Persky *et al.*, 2003). Both studies found powdered creatine products contained >99% creatine and did not note any unidentified peaks upon liquid chromatography.

3. FUTURE DIRECTIONS

The majority of information regarding the safety of creatine supplementation is available from relatively small clinical studies that lasted short periods of time, and examined healthy volunteers. Studies involving patients, larger numbers of subjects, long periods of time, and over a dose range are lacking. Investigators should assess and report on adverse events even by simple questionnaire. If possible, conclusions should be drawn whether adverse events were likely or unlikely related to the treatment. In addition, blood or muscle creatine levels should be evaluated to help relate adverse events to a systemic concentration of creatine, which could help assess whether side effects are dose-related. Finally, placebo controls allow judgments to be made whether the use of creatine is more likely to cause an adverse event than in the un-supplemented condition. For example, Table 4 summarizes adverse events from a study in patients with amyotrophic lateral sclerosis treated with creatine (Groeneveld *et al.*, 2005). The use of a placebo group allows conclusions to be drawn based on a potentially increased risk of a certain side effect. Muscle cramps

Table 4. Percentage of ALS patients who had an adverse event. Time average ratio indicates the relative prevalence of adverse events during the study. 1.0 = equal prevalence in the creatine (Cr) and placebo groups (Pl); < 1.0: less events in the creatine group; > 1.0: more events in the creatine group. Data adapted from Groeneveld *et al.* (2005) .

System	Event	Treatment	1 month	2 months	4 months	8 months	12 months	At any time	Time Average Ratio
Muscle	Cramps	Pl	61	70	79	69	73	91	
		Cr	62	73	78	73	67	95	1.0
	Cramps on	Pl	37	33	28	38	45	62	
	Exertion	Cr	24	36	38	42	38	70	1.1
	Limb Edema	Pl	18	9	18	29	45	46	
		Cr	21	26	35	42	42	54	1.4
Gastrointestinal	Nausea	Pl	13	7	7	7	14	24	
		Cr	6	6	9	9	8	23	0.99
	Vomiting	Pl	2	4	0	4	9	10	
		Cr	3	3	3	0	8	10	0.76
	Diarrhea	Pl	11	8	8	9	9	24	
		Cr	14	3	9	13	17	35	1.3
	Constipation	Pl	11	9	16	22	23	35	
		Cr	15	4	9	22	42	38	1.1
	General	Pl	11	7	8	4	5	18	
	Discomfort	Cr	3	6	6	9	13	19	1.4
	Reflux	Pl	7	12	15	16	9	27	
		Cr	12	9	7	13	17	28	0.85
Skin	Rash	Pl	6	7	7	20	23	24	
		Cr	5	8	7	13	13	19	0.71
	Pruritus	Pl	7	8	25	27	23	35	
		Cr	13	13	15	18	33	24	0.85

appear to be equally likely in this patient population whether on creatine or placebo whereas general gastrointestinal discomfort appears more prevalent in the creatine group.

4. CONCLUSION

The available data suggest that there are few adverse effects associated with creatine supplementation when ingested at recommended doses. Anecdotally, muscle dysfunction appears to be commonly associated with creatine supplementation, but data do not support this. Additionally, anecdotal reports of an association between creatine supplementation and impaired thermoregulation or dehydration are not supported by data. Although case reports suggest possible renal related side effects, most clinical studies show no indication of renal dysfunction with creatine use. As creatine supplementation becomes increasingly used as a potential intervention in clinical populations, larger scale studies should provide useful information into potential side effects, their severity and their incidence rate.

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