

Side Effects of Creatine Supplementation in Athletes

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Context: Allegations about side effects of creatine supplementation by athletes have been published in the popular media and scientific publications. **Purpose:** To examine the experimental evidence relating to the physiological effects of creatine supplementation. **Results:** One of the purported effects of oral creatine supplementation is increased muscle mass. A review of the literature reveals a 1.0% to 2.3% increase in body mass, which is attributed to fat-free mass and, more specifically, to skeletal-muscle mass. Although it is unlikely that water retention can completely explain these changes, increase in muscle-protein synthesis has never been observed after creatine supplementation. Indirect evidence based on mRNA analyses suggests that transcription of certain genes is enhanced. Although the effect of creatine on muscle-protein synthesis seems irrefutable according to advertising, this allegation remains under debate in the scientific literature. The kidneys appear to maintain their functionality in healthy subjects who supplement with creatine, even over several months. **Conclusion:** The authors, however, think that creatine supplementation should not be used by an individual with preexisting renal disease and that risk should be evaluated before and during any supplementation period. Even if there is a slight increase in mutagenic agents (methylamine and formaldehyde) in urine after a heavy load of creatine (20 g/day), their excretion remains within a normal range. No data are currently available regarding the potential production of heterocyclic amines with creatine supplementation. In summary, the major risk for health is probably associated with the purity of commercially available creatine.

Key Words: body composition, resistance training, kidney, skeletal muscle, liver

Concerns about the deleterious consequences of oral creatine supplementation were initiated in 1998 when 2 British nephrologists published a paper titled "Renal dysfunction accompanying oral creatine supplements" in *The Lancet*.¹ They reported the case of a 25-year-old man having suffered 8 years of a focal segmental glomerulosclerosis and presenting frequent nephrotic relapses. For the preceding 5 years the patient had required treatment with cyclosporine, a well-known

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nephrotoxic drug. As a soccer player, he started to ingest creatine in mid-August 1997 at a dose of 5 g 3 times per day for 1 week, followed by a maintenance dose of 2 g/d for 7 weeks. His glomerular filtration rate dropped by 50%. The reduced rate indicated an impaired kidney, which was gradually restored to normal function 1 month after the athlete stopped the supplementation. Three days after this publication the famous French sport newspaper *L'Equipe* (April 28, 1998) claimed that creatine is harmful for anyone in any condition. This news was quickly spread around the world by various media agencies, generating concern among athletes who consumed creatine on a regular basis. A few weeks later, we reported in the same journal that no adverse effects of creatine on kidney function were evident in a group of young healthy adults who supplemented over a period of 9 weeks.² This outcome indicated that the observation of Pritchard and Kalra¹ should not be generalized to all creatine consumers. Nonetheless, this particular case shed light on a potential deleterious side effect of creatine supplementation in athletes.

The controversy surrounding the deleterious side effects of creatine supplementation appeared again in 2001 when the French Agency for Food Safety published a report in which it presented creatine as a mutagenic and carcinogenic agent.³ At that time, there was no scientific evidence to support the agency's allegations, which were based on a theoretical model of creatine degradation.

A few years ago, the Web site of the US FDA (Food and Drug Administration) displayed a list of complaints reported by consumers or health-care professionals regarding creatine supplementation. A Web search for October 1998 revealed 32 matches for dyspnea, fatigue, grand mal seizure, intracerebral hemorrhage, vomiting, diarrhea, nervousness and anxiety, polymyositis, myopathy, rhabdomyolysis, severe stomach cramps, deep-vein thromboses, atrial fibrillation, cardiac arrhythmia, chest pain, and even death! Meanwhile, the FDA asked the public to keep in mind that there was "no certainty that a reported adverse event can be attributed to a particular product or ingredient. The available information might not be complete enough to make this determination." In other words, there was no scientific evidence to correlate oral creatine supplementation with any of these reported adverse effects. The FDA has now removed this page from its Web site.

Debate on the side effects induced by creatine supplementation is often based on emotional arguments rather than on rationality. To draw clear recommendations for safe use of creatine in athletes, we reviewed the scientific evidence on the possible side effects induced by creatine consumption in humans. The reader should keep in mind that the goal of this review is not to examine the efficiency of creatine supplementation for sport performance. Details on the ergogenic effects of creatine are available elsewhere.^{4,5}

Total Body Mass

One of the purported side effects of oral creatine supplementation regularly mentioned by consumers is increased total body mass, particularly muscle mass. On scientific grounds, the situation is less clear. Indeed, the average increase in body mass reported in the literature amounts to 1 to 2 kg, or 1% to 2.3% of total body mass (for a review, see Terjung et al⁵). Nevertheless, about 30% of published articles do not report any change in body mass (for example, McConell et al⁶ and

Peyrebrune et al⁷). Tentative explanations put forward for this apparent discrepancy between results focus on the characteristics of the subjects and the supplementation protocol. Sedentary people, physically active individuals, and recreational athletes seem to respond equally to oral creatine supplementation. Individuals need not follow a specific resistance-training program to increase body mass in response to oral creatine supplementation,⁸ although such a program potentiates the effects of creatine.⁹ Increases in body mass have been reported in both men⁸ and women,¹⁰ as has a lack of changes.^{10,11} Differences by sex have not been systematically studied. For instance, studies neither controlled for menstrual cycle nor reported any procedure to prevent subjects from otherwise affecting their own body mass during the supplementation period. Therefore, it is hazardous to speculate any dependence on sex. The duration of the supplementation does not seem to influence the presence of significant changes in body mass. Indeed, the proportion of studies reporting an effect on body mass is similar between short-term (<10 days) and medium-term studies (>10 days).¹² Presently, we have no convincing argument to explain why about 30% of the studies do not report any change in body mass after creatine supplementation.

Fat-Free Mass

A dozen studies have investigated changes in fat-free mass after creatine supplementation (eg, Willoughby and Rosene⁹ and Vandenberghe et al¹⁰). Ninety percent of these studies reported a higher increase in fat-free mass than in total body mass. The increase might even reach 6% after sustained creatine supplementation.

The increase in fat-free mass could be attributed more specifically to change in muscle mass. There are a few recent studies that investigated changes in muscle volume using either anthropometric dual-energy X-ray absorptiometry (DEXA) or magnetic-resonance imaging (MRI) techniques after creatine supplementation.^{9,13-16} In most cases, a direct effect on muscle volume was observed, with a mean increase of 12% when supplementation and training were maintained for several weeks. Thus, one might conclude that oral creatine supplementation has a direct effect on muscle mass. This increase might be a result of water retention in muscle or of increases in dry matter, possibly glycogen and proteins.

Hultman et al¹⁷ suggested that the increase in body mass during acute creatine supplementation is attributable to water retention because they observed a 0.6-L decline in urinary volume after ingestion of creatine 20 g for 6 days. Based on this indirect evidence, the notion that creatine supplementation increases muscles' water content has been widely accepted. Nonetheless, the mechanisms by which creatine supplementation could increase intracellular water remain unclear. Creatine is a highly polar molecule that plays a major role in regulating osmolarity in the cells. Without exchange of other ions, an increase in creatine content should increase cellular osmolarity and, consequently, intracellular water volume. When exposed to an osmotic shock, cells respond initially by a rapid swelling, followed after a few seconds by active extrusion of intracellular osmotically active solutes such as inorganic ions or organic molecules. This second phase is called the regulatory volume decrease. Assuming a 20% higher creatine content after supplementation, the osmolarity of the cell increases by only 2% to 3%, a change that should be

easily controlled by regulatory volume decrease. A second possible explanation is based on the fact that the entry of creatine into muscle sarcoplasm is governed by a Na^+ -dependent transporter.¹⁸ Nevertheless, considering the high activity of Na^+ - K^+ pumps, it is unlikely that intracellular Na^+ concentration is significantly affected by creatine supplementation. Another explanation involves a higher glycogen content ($\approx 25\%$) observed when creatine supplementation is combined with resistance training.¹⁹ While stored in skeletal muscle, 1 g of glycogen is accompanied by 2 to 3 g of water, which could explain an increase in water muscle content of ≈ 300 g.

In 1999 we measured changes in intracellular and extracellular water volumes (by multifrequency bioimpedance) in subjects undergoing creatine supplementation over a period of 9 weeks.²⁰ Although body mass increased by 2 kg, the relative volume of body-water compartments was not affected, suggesting that the increase in body mass after creatine supplementation cannot be attributed to water retention but is probably caused by proportionate increases in dry matter.

Skeletal-Muscle Mass

Most, if not all, commercial and anecdotal claims of the beneficial effects of creatine supplementation center on the increase in skeletal-muscle protein mass. Several scientific publications also emphasize the higher content of muscle proteins by association with the increases in body mass or fat-free mass. The pertinent question for researchers and practitioners is whether there is sufficient experimental evidence to support these claims.

Parise et al²¹ studied the effect of acute creatine monohydrate supplementation on muscle-protein synthesis in fasted adult human subjects. Young, healthy men and women were allocated to creatine (20 g/d for 5 days followed by 5 g/d for 4 days) or placebo. The rate of incorporation of infused ^{13}C -leucine into the protein pool was measured. These authors concluded that there was no substantial increase of muscle-protein synthesis under creatine supplementation. To determine whether feeding is required to allow creatine to stimulate protein synthesis, we have used a similar technique to measure creatine levels in the vastus lateralis in fasted and fed states before and after creatine supplementation (21 g/d for 5 days). We have also quantified muscle-protein breakdown in the forearm by arteriovenous differences in L- $[\text{}^2\text{H}_5]$ -phenylalanine.²² Feeding led to a doubling of protein synthesis and a 40% depression of muscle-protein breakdown, but no effect of creatine monohydrate was found. We further examined the possible stimulatory effect of creatine loading (21 g/d for 5 days) in conjunction with acute resistance exercise on an isokinetic dynamometer (20 \times 10 repetitions of leg extension–flexion at 75% of 1-repetition maximum, before and after creatine intake).²³ Exercise increased the synthesis rates of myofibrillar and sarcoplasmic proteins by twofold to threefold, and protein breakdown diminished, but creatine loading had no anabolic effect. Clearly, both exercise and food are much stronger stimuli for protein synthesis than creatine intake is in healthy adult individuals.

A few recent studies used different molecular-biology techniques to investigate muscle-specific gene expression and regulatory signals of protein synthesis. Willoughby and Rosene⁹ investigated the effect of oral creatine on myosin heavy-chain

expression in adult male subjects after resistance training. The results of 12 weeks of resistance training showed that the expression of myosin heavy-chain mRNA was increased more substantially in the group receiving creatine than in the group receiving a placebo. In addition, Deldicque et al²⁴ investigated the effect of creatine supplementation on insulinlike growth factor (IGF-I and IGF-II) mRNA expression, including the PI3K-Akt/PKB-mTOR-signaling pathway, in adult human skeletal muscle. IGF-I and IGF-II mRNA were slightly, but significantly, increased after creatine supplementation (5 days, 21 g/day). IGFs stimulate the PI3K-Akt/PKB-mTOR-signaling pathway, which is involved in the regulation of skeletal-muscle fiber size and stimulation of translation initiation by activating the mammalian target of rapamycin (mTOR) and 2 of its downstream effectors, namely, p70^{s6k} and 4E-BP1 (eukaryotic initiation factor-4E binding protein-1). The subjects underwent a resistance-exercise session consisting of a 1-leg knee extension, and muscle biopsies were taken before and after the exercise test. Although resistance exercise was shown to increase both IGF-I and IGF-II mRNA, creatine did not potentiate this effect. Three hours after stopping the exercise, creatine supplementation did not induce any change in p70^{s6k} or 4E-BP1 expression as compared with placebo treatment. The phosphorylation of the 4E-BP1 factor, however, displayed a slight increase at 24 hours postexercise under the creatine-supplementation condition. Willoughby and Rosene²⁵ reported a positive effect of oral creatine and resistance training on key myogenic regulatory factor expression. Their study suggested that 12 weeks of creatine supplementation, in conjunction with heavy resistance training, increased the mRNA expression of muscle creatine kinase by way of a pretranslational mechanism, likely because of the concomitant increases in the expression of myogenin and MRF4 (myogenic regulatory factor 4).

Olsen et al²⁶ recently investigated the influence of creatine-monohydrate (6 to 24 g/d) or protein (20 g/d) supplementation on satellite-cell density and myonuclei number in healthy adult men during 16 weeks of heavy resistance training. The results of this study showed that, after 16 weeks of training, mean muscle-fiber area increased by 17% after creatine supplementation, 8% after protein supplementation, and 4% in a placebo group. The author concluded that creatine supplementation in combination with strength training amplifies training-induced increases in satellite-cell number and myonuclei concentration in adult human skeletal fibers, facilitating enhanced muscle-fiber growth in response to strength training.

Hespel and colleagues²⁷ investigated the effect of creatine supplementation on muscle recovery during rehabilitative strength training. Casts were used to immobilize the right legs of their volunteers for 2 weeks. Thereafter, the subjects participated in a knee-extension rehabilitation program for 10 weeks. Immobilization decreased quadriceps-muscle cross-sectional area by 10% and maximal power output by 25% by the same magnitude in the creatine and placebo conditions. During rehabilitation, cross-sectional area and maximal power output recovered more quickly with creatine. Muscle biopsies were also taken before and after immobilization, as well as after the rehabilitation program. Immobilization did not change myogenic-factor protein expression. After rehabilitation, myogenin was increased in placebo but not in creatine, though, whereas MRF4 was increased in creatine but not in placebo. The change in MRF4 expression was correlated with the change in mean muscle-fiber diameter. These results indicate that creatine does not affect muscle wasting induced by immobilization but stimulates muscle

regrowth during rehabilitative strength training. This effect appears to be mediated by MRF4 and myogenin expression.

In conclusion, despite the activation by some muscle signals, creatine supplementation does not seem to have induced a significant increase in protein synthesis or a decrease in muscle proteolysis.

Muscle Cramps

Anecdotal reports from athletes have claimed that creatine supplementation might induce muscle cramps. The prevalent explanation for this potential side effect is an imbalance in muscle electrolytes. Kreider et al,²⁸ however, investigated athletes involved in heavy resistance training (5 h/d) for 28 days. The athletes supplemented daily with 15.75 g of creatine monohydrate. There was no evidence of muscle cramping during resistance-training sessions or during performance trials. Along the same line, Vandenberghe et al¹⁰ pursued a study on sedentary female subjects who were involved in a 10-week resistance-training program with creatine supplementation (20 g/d for 4 days, then 5 g/d up to 10 weeks). No spontaneous side effects were reported during the entire duration of the study. Nevertheless, Juhn and colleagues²⁹ reported muscle cramping in 25% of 52 baseball and football players who supplemented with 6 to 8 g/d during 5 months and 3 months, respectively. Later studies on 96 young healthy subjects trained over 3 years³⁰ and 10 older men involved in resistance training reported no cramping associated with creatine supplementation.³¹

The anecdotal reports of muscle cramps might be related to the intensity of exercise rather than creatine supplementation. Keeping athletes well hydrated could reduce this risk. Moreover, psychological stimulation could lead an individual to exercise over his or her optimal intensity. Further epidemiological studies should be conducted to clarify the potential side effects of muscle cramping with creatine supplementation.

Gastrointestinal Complaints

There have also been some anecdotal claims that creatine supplementation evoked gastrointestinal distress (stomach upset, vomiting, diarrhea) in consumers of oral creatine, but these assertions are not supported by scientific evidence. The literature lacks precise information on this matter. Nevertheless, one report from Vandenberghe et al³² stated that one third of their subjects (3/9) had minor gastrointestinal distress during 3 days of creatine ($0.5 \text{ g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$) and caffeine (400 mg/d) supplementation. In addition, Juhn et al²⁹ reported diarrhea in 31% of their baseball and football players who supplemented with 6 to 8 g of creatine monohydrate during 5 and 3 months of training, respectively. These authors suggested that this side effect might be the result of the unusually high osmotic load imposed on the digestive tract of some subjects. On the contrary, Kreider et al²⁸ did not observe any disturbances in their subjects. Greenhaff³³ supported this observation, with his sample ingesting 20 g of creatine per day. Greenhaff reported, however, that some discomfort can occur if creatine is incompletely dissolved before ingestion. Athletes and coaches should be reminded to ensure that creatine is well dissolved before ingestion.

Liver Dysfunction

Despite the allegations published in sports newspapers and periodicals, there is little scientific information on liver-metabolism changes induced by oral creatine supplementation. Some publications have reported data on liver function in individuals taking creatine supplements.^{34,35} No changes in enzyme levels were observed during supplementation. Additional information was obtained after oral creatine supplementation in trained subjects.¹² No statistical differences were observed throughout the study as far as alkaline phosphatase, aspartate transaminase, alanine transaminase, and gamma glutamyl transpeptidase were concerned. Thus, there is no reason to believe that oral creatine supplementation would induce changes in liver function in healthy human subjects.

Kidney Impairment

Creatine load (from 2 to 20 g/d) seems to be totally absorbed by the intestinal tract. Skeletal muscle cannot take up all this excess, so a large amount of ingested creatine is excreted in the urine (40% to 72%). The first investigations on renal function in healthy individuals who consumed oral creatine supplements were published 7 to 9 years ago.^{2,36,37} We compared renal clearances of creatinine, urea, and albumin in 3 different groups of active subjects who consumed creatine for 5 days, 9 weeks, and up to 5 years with the clearances in control groups. We did not observe statistical differences between the control and creatine groups. Lately, several other investigations have supported our primary results on glomerular-filtration rate. From these experiments we can state that glomerular-filtration rate and the tubular reabsorption process were not affected by oral creatine supplementation of the usual daily amount (20 g/d for 5 days, <5 g/d thereafter). Kreider et al,³⁴ in a large survey (98 subjects) on regular creatine users who consumed the supplement for 21 months, reached the same conclusion.

Furthermore, we did not observe any modification induced by creatine loading on urine albumin-excretion rate, which remained within the physiological range for healthy subjects. Microalbuminuria is a well-known predictor of kidney impairment. The excretion rate of plasma albumin in urine has been widely used to assess increased glomerular-membrane permeability in many pathological conditions. A subclinical increase in urinary albumin-excretion rate is a powerful predictor of renal failure. The upper level of albumin excretion in a healthy population under resting conditions is 20 µg/min. Under various conditions of oral creatine supplementation in healthy subjects, we never observed increased albumin excretion in comparison with a placebo investigation or a control population.^{2,36,37} Thus, we think that glomerular-membrane permeability is not affected by creatine-monohydrate supplementation in healthy subjects.

Nevertheless, in 1998, Pritchard and Kalra¹ introduced the first case of kidney damage induced after creatine supplementation. Koshy et al³⁸ published another case report of interstitial nephritis in a patient who had taken 20 g of creatine daily for 4 weeks. This previously healthy man presented a 4-day history of nausea, vomiting, and bilateral flank pain. He was hospitalized with a serum creatinine concentration of 2.3 mg/100 mL (normal upper range limit: 1.5 mg) and a urine protein excretion of 472 mg/d (normal upper range limit: 150 mg/100 mL). A renal

biopsy revealed acute focal interstitial nephritis and acute tubular injury. After the patient stopped taking creatine, his renal function became normal. This is only 1 case out of thousands of regular creatine consumers, but it emphasizes our recommendation to be tested regularly with urinalysis.

Five other anecdotal cases (abstract reports) have been published in the recent literature. To be modestly critical, however, we found these reports somewhat dubious despite the diagnosis of acute renal failure. The individual doses and duration were not reported for 3 individuals, and the other 2 might have consumed other unknown substances such as steroids. Thus, the absence of controlled experimentation precludes the (tentative) hypothesis that creatine supplementation induces kidney impairment in healthy subjects.

Mutagenicity and Carcinogenicity Risks of Excess Creatine Supplementation

Based on the excellent and comprehensive review by Wyss and Kaddurah-Daouk³⁹ on creatine and creatinine metabolism,³ the French Agency for Food Safety claimed unequivocally that excess consumption of creatine and creatinine might induce derived carcinogenic and mutagenic compounds that could put athletes and consumers of exogenous creatine at risk.³ Indeed, the excess conversion of creatine to sarcosine might result in cytotoxic agents such as methylamine. The latter has been found to be deaminated by semicarbazide-sensitive amine oxidase (EC 1.4.3.6) to produce formaldehyde and hydrogen peroxide. Methylamine and formaldehyde are well-known cytotoxic agents, the presence of which can be revealed by urine analysis. Formaldehyde has the potential to cross-link proteins and DNA, leading to cytotoxicity and carcinogenic effects in cells. The toxic aldehyde is related to different pathological conditions such as vascular damage, diabetic complications, and nephropathies.

Recently, we investigated 20 healthy young men who supplemented daily with 21 g creatine monohydrate for 14 days.⁴⁰ We collected 24-hour urine before and after creatine supplementation and measured creatine, creatinine, methylamine, formate, and formaldehyde concentrations. Table 1 presents the changes in urine excretion of formaldehyde, formate, and methylamine from before to after creatine supplementation. Twenty-four-hour urine output of methylamine and formaldehyde

Table 1 Mean Values (\pm SEM) of Urine Contents Before and After Creatine Supplementation, 21 g/d for 14 Days*

	Before creatine	After creatine
Methylamine (mg/24 h)	0.69 \pm 0.06	6.41 \pm 1.45 [†]
Formaldehyde (μ g/24 h)	64.78 \pm 16.28	290.4 \pm 66.3 [†]
Formate (mg/24 h)	12.46 \pm 1.04	14.16 \pm 1.84
Albumin (mg/24 h)	9.78 \pm 1.93	6.97 \pm 1.15

*Adapted from Poortmans et al.⁴⁰

[†] $P < .001$ between values before and after creatine supplementation.

increased 9.2-fold and 4.5-fold, respectively ($P < .001$) after creatine feeding, with no increase in formate excretion. There was no correlation between plasma creatine and urine methylamine ($r^2 = .025$, $P =$ not significant) or formaldehyde ($r^2 = .017$, $P =$ not significant).

The results of our investigation indicate that short-term oral creatine supplementation in healthy subjects enhances the mechanisms leading to the conversion of creatine to sarcosine and then to methylamine, the latter giving rise to formaldehyde. The conversion of formaldehyde to formate should be rather rapid in cells, the latter product representing indirectly the production of the former substrate. Using rat and mice models, Yu and Deng⁴¹ demonstrated that *in vivo* deamination of methylamine produces formaldehyde and hydrogen peroxide, which are both recognized as cytotoxic substances. Consequently, they hypothesized that chronic administration of large quantities of creatine as an ergogenic supplement would increase the production of methylamine and subsequently formaldehyde, both being potentially cytotoxic. Our results support this mechanism in humans.

Nevertheless, the 9.2-fold increase in methylamine urine excretion induced by creatine ingestion did not reach the normal upper-limit values from healthy humans, up to 35 mg/d (mean \pm 3 SD). After creatine supplementation, urine formate excretion also remained below the upper range (14 to 20 mg/d) reported in healthy subjects. Under creatine supplementation, however, the urine excretion of formaldehyde increased by 4.5-fold.

Because creatine is transformed to sarcosine by microbial enzymatic reactions, it is likely that methylamine is formed in the intestine and therefore might damage the intestinal epithelium. Methylamine is toxic to human endothelial cells and forms patchlike lesions and even kidney damage. In mammals, semicarbazide-sensitive-amine-oxidase activity has been found in various tissues associated with the vascular system. Therefore, it is likely that the deamination of methylamine occurs in the circulation. It is possible that this flooding of methylamine in blood, together with semicarbazide-sensitive amine oxidase, might produce formaldehyde, which could favor microangiopathy in the renal glomeruli, but we did not observe any of these outcomes in these subjects.⁴⁰

Even if deleterious systemic effects were not apparent, we cannot exclude the possibility that a systematic production of low extra doses of cytotoxic agents could induce nephropathy. Clearly, epidemiological data are required to evaluate potential risks over a larger cohort of individuals. The results of the present investigation suggest that medical supervision should be considered if athletes wish to use high doses of creatine over extended periods of time. Kidney function of subjects who supplemented with creatine on a regular basis should be systematically monitored throughout the ingestion period.

The negative opinions on oral creatine supplementation center on the purported carcinogenic effect of creatine. Based on current knowledge, the probability that nitrosation products of creatine are formed in the stomach to any significant extent is close to zero. A very recent short publication by Derave and colleagues⁴² supports this conclusion. In a double-blind, placebo-controlled study, these authors investigated the urinary excretion of N-nitrososarcosine after 1 week of high-dose (20 g/d) and 20 weeks of low-dose (5 g/d) creatine supplementation in healthy humans. They concluded that creatine ingestion does not increase the urinary excretion of the carcinogen N-nitrososarcosine.

Wyss and Kaddurah-Daouk³⁹ reported in a review that food processing, in particular frying and broiling meat, is associated with the generation of mutagenic and carcinogenic substances, namely, the amino-imidazo-azaarenes products that we shall call the heterocyclic amines for simplicity. Identifying heterocyclic amines in human urine is not an easy procedure. The analytical methods involve solid-phase extraction and quantification by combined liquid chromatography and tandem mass spectrometry to identify the major heterocyclic amines in urine. Nevertheless, investigators will have to quantify this potential risk to definitively prove or disprove the alleged carcinogenic risks of creatine supplementation.

To conclude, our investigation shows that short-term, heavy-load oral creatine supplementation stimulates the production of an excess of methylamine and formaldehyde in the urine of healthy humans. Even though the production of cytotoxic agents had no apparent effect on the kidney function of volunteers in this study, long-term and epidemiological data are essential to assess whether creatine supplementation is harmless in all healthy individuals under all conditions in the competitive athletic setting.

Practical Recommendations

The purpose of this brief review was to summarize the scientific literature and present recommendations about the potential side effects of oral creatine supplementation in healthy individuals. Despite articles and editorials published in the general and sports media, there have been no real incidents of muscle cramps, gastrointestinal discomfort, or liver impairment after regular loads of oral creatine.

In addition, there is no apparent kidney dysfunction in healthy individuals who take oral creatine monohydrate in the recommended daily amounts (20 g for 5 days, 3 to 5 g thereafter). Nevertheless, the amount ingested should never exceed the recommended doses. The few case reports of renal incidents have not been corroborated in larger experimental studies, but it would be prudent for athletes, coaches, and practitioners to remain cautious. Regular nutritional and medical support should be an elementary strategy to reduce the risk of potential dysfunction. The analysis of urinary albumin-excretion rate (<20 $\mu\text{g}/\text{min}$) appears to be the most simple, inexpensive, accurate test to assess any early incidence of kidney impairment. This test should be done under resting conditions, that is, at least 24 hours after the last physical activity. If the primary-care physician has any concerns, the athlete should be referred to a nephrologist. We recommend that urinary albumin level be analyzed on systematic basis before and a few days after beginning supplementation, as well as every 3 months, in the case of a chronic intervention. We advise that creatine supplementation not be used by athletes with preexisting renal disease or those with a potential risk for renal dysfunction. Medical advice should be sought if there are any doubts on the suitability of creatine supplementation for individual athletes. Great care should also be taken as far as the purity of commercially available exogenous creatine supplements is concerned. Analytic tests must prove their unique nutraceutical composition, as safety is not ensured with every preparation.

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