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REVIEW ARTICLE

Studies on the safety of creatine supplementation

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Abstract Doubtful allegations of adverse effects of creatine supplementation have been released through the press media and through scientific publications. In the present review we have tried to separate the wheat from the chaff by looking for the experimental evidence of any such claims. Anecdotal reports from athletes have appeared on muscle cramp and gastrointestinal complaints during creatine supplementation, but the incidence of these is limited and not necessarily linked to creatine itself. Despite several unproved allegations, liver (enzymes, urea) and kidneys (glomerular filtration urea and albumin excretion rates) show no change in functionality in healthy subjects supplemented with creatine, even during several months, in both young and older populations. The potential effects (production of heterocyclic amines) of mutagenicity and carcinogenicity induced by creatine supplementation have been claimed by a French Sanitary Agency (AFSSA), which might put consumers at risk. Even if there is a slight increase (within the normal range) of urinary methylamine and formaldehyde excretion after a heavy load of creatine (20 g/day) this is without effect on kidney function. The search for the excretion of heterocyclic amines remains a future task to definitively exclude the unproved allegation made by some national agencies. We advise that high-dose (>3–5 g/day) creatine supplementation should not be used by individuals with pre-existing renal disease or those with a potential risk for renal dysfunction (diabetes, hypertension, reduced glomerular filtration rate). A pre-supplementation investigation of kidney function might be considered for reasons of safety, but in normal healthy subjects appears unnecessary.

Keywords Sport · Creatine · Liver · Kidney · Health risks

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Introduction

Concerns about the deleterious effects of oral creatine supplementation were initiated in Spring 1998 when two British nephrologists published a paper in "The Lancet" suggesting that there is "strong circumstantial evidence that creatine was responsible for the deterioration in renal function" (Pritchard and Kalra 1998). That same year, the potential adverse effects of oral creatine supplementation were critically reviewed by Juhn and Tarnopolsky (1998) who concluded that future studies should include large randomized controlled trials to evaluate the short- and long-term effects related to the renal and hepatic systems, as well as the many other organ systems in which creatine plays a metabolic role. The "Food and Drug Administration (FDA)" on its website declared that "there is no certainty that a reported adverse event can be attributed to a particular product or ingredient. The available information (on creatine) may not be complete enough to make this determination". However, the "Association of Professional Team Physicians" and the "American College of Sports Medicine" (American 2000) concluded that much more long-term research needs to be done (on creatine) before one can

issue a verdict on its health status. In 2004, a Scientific Panel of the "European Food Safety Agency (EFSA)" reported that "the safety and bioavailability of creatine, creatine monohydrate, in food for particular nutritional uses, is not a matter of concern provided there is adequate control of purity of this source of creatine" (European 2004). Nevertheless, that same year, a report of the "Agence Française de Sécurité Sanitaire et Alimentaire (AFSSA)" claimed that "one should not encourage publicity of creatine in order to protect participants in sport to any potential pathological consequences" (Agence 2004). Eventually, a world expert on creatine metabolism, Wyss (2004), stated that there are still many open questions related to creatine metabolism which are worth being analyzed in detail.

To sum up these reports, there are still several uncertainties on the health hazards of chronic or long term creatine supplementation in sports events or training.

Muscle cramp incidences

Anecdotal reports from athletes have claimed that creatine supplementation may induce muscle cramps and dehydration. The prevalent hypothesis to explain this potential side effect is an imbalance in muscle electrolytes. However, in athletes supplemented daily with 15.75 g of creatine monohydrate and involved in heavy resistance training for 28 days (Kreider et al. 1998) no evidence was found of muscular cramping during resistance training sessions or during performance trials. Similarly, Vandenberghe et al. (1997) undertook a study on sedentary female subjects who were involved in a 10-week resistance training programme with creatine supplementation (Vandenberghe et al. 1997); again no spontaneous side-effects were reported during the entire duration of the study. Two further studies on 96 young healthy subjects trained during 3 years, and 10 older men involved in resistance training, found no evidence of cramping with creatine supplementation (Greenwood et al. 2003; Gotschalk et al. 2002). A more recent review concluded that media claims and anecdotal reports on muscle cramps are not related to exogenous creatine intake (Dalbo et al. 2008).

Muscle cramping might be due to the intensity of exercise rather than creatine supplementation, and maintaining a well-hydrated status could reduce this risk. Meanwhile, further epidemiological studies should be performed to evaluate this potential side effect in hot and/or humid conditions.

Gastrointestinal complaints

A number of claims of gastrointestinal distress (stomach upset, vomiting, and diarrhoea) among consumers of creatine have been made despite a lack of precise information in the scientific literature. Some reports have even stated that one-third of their subjects (3/9) had minor gastrointestinal distress during 3 days of creatine (40 g/day) and caffeine (400 mg/day) supplementation (Vandenberghe et al. 1997). In addition, Juhn et al. (1999) reported diarrhoea in 31% of baseball and football players studied who were supplemented with 6–8 g/day of creatine monohydrate during 5 (baseball) and 3 (football) months, respectively. These authors suggested that this side effect may be the result of an unusually high osmotic load being imposed on the digestive tract in some subjects. In contrast no gastrointestinal tract disturbances were observed by Kreider et al. (1998) and Greenhaff (1998) in subjects supplemented with 20 g of creatine per day. It was suggested that some gastrointestinal distress might happen when a single serving of more than 10 g of creatine is given to some athletes (Ostojic and Ahmetovic 2008). However, this discomfort is possibly the result of the creatine being incompletely dissolved before ingestion.

In conclusion, there is insufficient evidence to support the notion that creatine supplementation has a detrimental effect on the gastrointestinal tract.

Liver dysfunctions

Allegations published in sports newspapers and periodicals have questioned the safety of creatine supplements on liver function. No statistical evidence in support of this was found in the previous studies using different dose/duration combinations (20 g daily for 5 days or up to 10 g daily for 5 years) through measurements of alkaline phosphatase, aspartate transaminase, alanine transaminase and gamma glutamyl transpeptidase (see reviews in Poortmans and Francaux 2000, 2008). On this basis it seems unlikely that oral creatine supplementation has any deleterious effects on liver function in healthy human subjects.

However, a study reported that mice supplemented with oral creatine for 6 days increased liver protein content by 23%, as well as increasing aspartate transaminase and alanine transaminase (Duarte et al. 1999). Moreover, mice supplemented with creatine monohydrate for 8 weeks developed chronic hepatitis (Keys et al. 2001). However, Tarnopolsky et al. (2003) undertook a study to characterize pathological changes of intermediate- and long-term creatine monohydrate supplementation in mice and in rats. The administration of creatine monohydrate for 1 year to mice resulted in histological evidence of hepatitis without any evidence of pathology in a variety of other tissues and organs in healthy and transgenic (SOD1) mice and in normal rats. Whereas creatine administration to rats did not result in any pathology in any of the organs/tissues

examined. These results pointed to a species- and tissue-specific response to creatine supplementation.

Muscle fibre rupture

Phosphorylcreatine kinase (PCK) is commonly used in clinical pathology as a marker of muscle enzyme efflux and thus muscle fibre rupture. Contradictory results, however, have been recorded with creatine supplementation. Five publications failed to report any changes in total plasma PCK after 5–84 days of 5–20 g creatine/day supplementation (Almada et al. 1996; Engelhardt et al. 1998; Mihic et al. 1998; Rawson et al. 2001; Santos et al. 2004), even when this was associated with exercise-induced muscle damage and muscle soreness. In contrast Kreider et al. (1998) reported a mild elevation in PCK after 28 days of 15.75 g/day, but this was in athletes undergoing heavy training which alone might induce the observed level of muscle enzyme efflux.

Plasma PCK exists in three different isoforms, namely MM for skeletal muscle, MB for heart and BB for brain. Todate there are no reports available on the specific enzyme isoforms which are released from the tissues with creatine supplementation. Most probably, a slight increase observed in a few reports could be attributed to the skeletal muscle isoform, but precise information is needed to confirm this hypothesis.

Kidney impairments

The first study on creatine supplementation on two subjects was published in 1926 by Chanutin (1926). He found an increased excretion of creatinine as well as a significant, positive nitrogen balance. Two years later, Rose et al. (1928) reported a 22–25% increase in the creatinine excretion in one man and one woman after 49 days of feeding 1 g/day. These early studies were followed by few publications showing either little or no increase in creatinine excretion with creatine supplementation (Hyde 1942) or a 10–30% increase. Eventually, using oral [^{15}N] creatine feeding in humans, it was confirmed that urine is the only major excretory route for creatine and creatinine (Hoberman et al. 1948).

More recent publications on plasma levels of urea and creatinine with creatine supplementation (Poortmans and Francaux 2000, 2008) have failed to show any changes in plasma urea while up to 50% showed a mean increase of 15% in plasma creatinine. In spite of this there does not appear to be any relationship between the daily creatine load, or the duration of supplementation, and the observed (slight) increase in plasma creatinine; which remained within the normal range of the healthy population.

Numerous studies have been reported on the urine excretion of urea and creatinine after creatine supplementation (Poortmans and Francaux 2000, 2008). Some investigations have demonstrated an increase in creatinine excretion when individuals were fed with creatine, while others did not observe any statistical change in creatinine excretion after different durations of oral creatine supplementation in trained individuals. A few publications investigated the urine output, but the results are contradictory, showing either an increase (Bermon et al. 1998), a stable (Maganaris and Maughan 1998; Poortmans and Francaux 1998) or a decline in urinary output (Hultman et al. 1996). The latter suggested that the increase in body mass during acute creatine loading is likely to be attributable to body water retention (Hultman et al. 1996). Creatine (from 2 to 20 g a day) appears to be totally absorbed by the intestinal tract, but skeletal muscle cannot take up all of this and usually 40–72% of the original load is excreted.

Urea excretion was also examined in a few studies (Poortmans and Francaux 2000, 2008). No alteration in 24 h urea was observed after a few days to several years (5 years) of oral creatine supplementation. Therefore, it seems reasonable to state that the liver does not overproduce urea in healthy subjects supplemented with creatine.

The first investigations on renal function in healthy individuals who consumed creatine were published 13 years ago. Renal clearances of creatinine and urea in three different groups of active subjects who consumed creatine during 5 days, 9 weeks and up to 5 years were compared to control groups (Poortmans et al. 1997; Poortmans and Francaux 1998, 1999). There were no statistical differences between the control group and the creatine consumers. From these experimental protocols we can state that glomerular filtration rate and tubular reabsorption are not affected by oral creatine supplementation using the usual daily amount of 20 g daily for 5 days followed by 10 g/day or less thereafter. Very recently, we investigated the glomerular filtration rate using the assay of plasma Cystatin C in order to avoid the potential uncertainty of the creatinine clearance determination (Fig. 1). Glomerular filtration rate (ml/min) was calculated from plasma Cystatin-C determinations in individuals who regularly, and several days per week, ingested exogenous creatine during less than a year to several years. The control subjects were young athletes who had not previously taken creatine. All values are within the normal range for a clinically normal population.

From Fig 1 it seems reasonable to conclude that exogenous creatine does not impair the glomerular filtration rate in healthy subjects. These results confirmed the data on

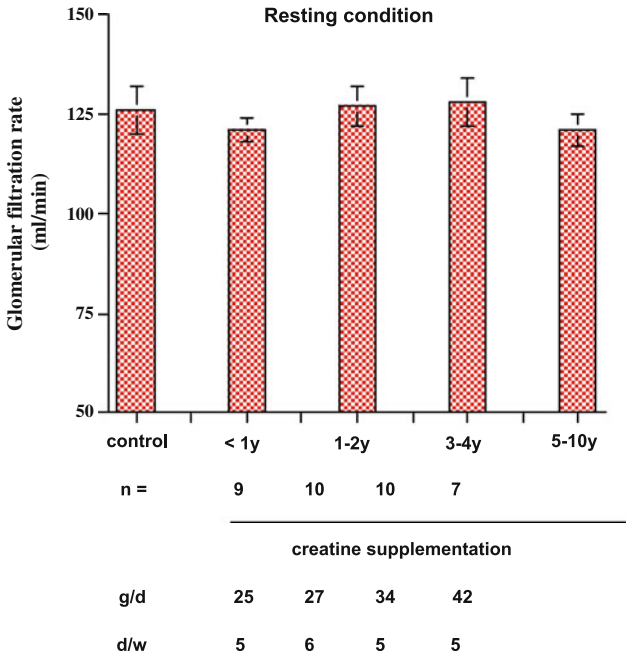

Fig. 1 Glomerular filtration rate (ml/min) calculated from plasma Cystatin-C determination among young athletes with no creatine supplementation (control) and individuals who regularly, several days per week, ingested exogenous creatine during less than a year to several years. All values are within the normal range for a clinically normal population. The number (*n*) of young individuals (mean age: 14–28 years), the daily quantity per day (g/day) and the number of days per week (day/week) of creatine supplementation are given for each category

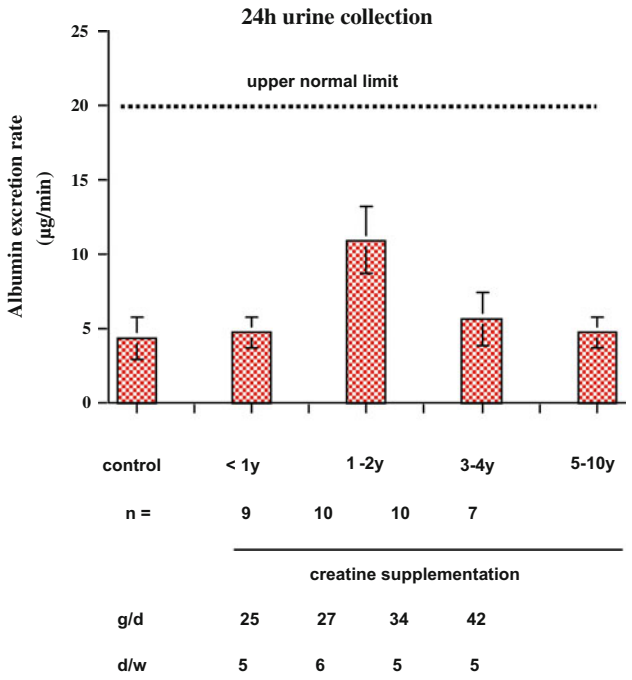

Fig. 2 Albumin excretion rate, calculated over a 24-h urine collection, among young athletes with no creatine supplementation (control) and individuals who regularly, several days per week, ingested exogenous creatine during less than a year to several years. None of these values reached the upper limit of a clinically normal population. The number (*n*) of young individuals (mean age: 14–28 years), the daily quantity per day (g/day) and the number of days per week (day/week) of creatine supplementation are given for each category

Cystatin-C reported by Gualano et al. (2008) in trained male athletes.

Microalbuminuria is a well-known predictor of kidney impairment (Evans and Greaves 1999). The excretion rate of plasma albumin in urine has been widely used to assess increased glomerular membrane permeability in many pathological conditions (Mogensen 1990; Mattock 1992; Camamori and Fioretto 2000). A sub-clinical increase in urinary albumin excretion rate is a powerful predictor of the later development of persistent proteinuria and renal failure. The upper level of albumin excretion in a healthy population under resting condition is 20 µg/min. The values we obtained under different conditions of oral creatine supplementation in healthy subjects are shown in Fig. 2.

An increase of albumin excretion was observed when compared to a placebo investigation or to a control population (Poortmans and Francaux 1999; Poortmans et al. 2005) but in all cases, values remained within the normal range for a clinically normal population. From this we conclude that the glomerular membrane permeability is not affected in healthy subjects by chronic supplementation up to several years of creatine monohydrate.

In order to clarify the potential impairment of kidney function by chronic creatine supplementation, studies have also been conducted using animal models and humans with initial nephropathies.

Animal studies

The Han: Sprague–Dawley Renal Disease-cy rat is well-documented and accepted as an animal model of inherited renal cystic disease that resembles human autosomal dominant polycystic kidney disease. Five weeks of creatine supplementation increased disease progression and worsened renal function in the animal model of kidney disease (Edmunds et al. 2001). However, this conclusion on inherited renal cystic disease in rats was not confirmed by other nephrologists (Taes et al. 2003). In another study, animals were allocated to four experimental groups: (1) sham-operated, normal diet; (2) sham-operated, creatine diet; (3) renal failure (two-thirds nephrectomized), normal diet; (4) renal failure (two-thirds nephrectomized), creatine diet. The study did not demonstrate any deleterious effect of creatine supplementation on kidney function in normal rats, or in animal models with pre-existing moderate renal dysfunction, as evidenced by the lack of changes in serum creatinine, urea, 24 h urinary albumin excretion and glomerular filtration rate.

A 40% reduction in resting renal blood flow and glomerular filtration rate with creatine versus control, with no modification of 24-h urinary protein excretion, was observed after 10 weeks of creatine supplementation in endurance-trained healthy rats (Ferreira et al. 2005). The authors concluded that creatine alone induced an important and significant reduction of both renal plasma flow and glomerular filtration rate. However, opposite results were obtained by Taes et al. (2003) who used three different methods to measure glomerular filtration rate, in addition to albumin excretion rate.

Human nephropathies

In 1998, Pritchard and Kalra (1998) reported the first case of kidney damage induced by creatine supplementation. The 25-year-old man who had required treatment with cyclosporin, a certified nephrotoxic drug, for the previous 5 years to minimize nephrotic relapses, presented a focal segmental glomerulosclerosis with frequently relapsing steroid-response nephrotic syndrome. A soccer-trained individual, who had started to load creatine in mid-August 1997 with 5 g creatine monohydrate three times per day for 1 week and then a maintenance dose of 2 g/day for 7 weeks, had his glomerular filtration rate dropped by 50%. The glomerular filtration rate was gradually restored to normal after 1 month of stopping creatine supplementation.

A further case report of interstitial nephritis was published by Koshy and Griswold Schneeberger (1999). A patient who had previously been healthy presented a 4-day history of nausea, vomiting and bilateral flank pain after 20 g of creatine daily for 4 weeks. The patient was hospitalized with a serum creatinine concentration of 2.3 mg/100 ml (normal upper range limit: 1.5 mg) and a urinary protein excretion of 472 mg/day (normal upper range limit: 150 mg). A renal biopsy revealed acute focal interstitial nephritis and acute tubular injury. After stopping the creatine supplements his renal function subsequently became normal. This is an anecdotal case out of thousands of regular creatine consumers. Nevertheless, it emphasizes our recommendation to test regularly urinalysis (see below).

A few more anecdotal cases (abstract reports) have appeared in the recent literature (Poortmans and Francaux 2008). However, these reports are dubious despite the diagnosis of acute renal failure. For three individuals the doses and durations of creatine given are not reported and for the remaining two individuals there is the possibility of other unknown substances (steroids?) being consumed. The absence of any controlled values seriously limits any conclusion that creatine supplementation results in impairment of kidney function in healthy subjects.

Importantly, long term (310 days) creatine supplementation (10 g/day) in 57 patients with neurodegenerative disease amyotrophic lateral sclerosis did not lead to any increase of plasma urea levels or to a higher prevalence of micro-albuminurea (<20 μg/min) (Groeneveld et al. 2005).

Mutagenicity and carcinogenicity risks of excess creatine supplementation

Methylamine and formaldehyde production

Based on an extended review of creatine and creatinine metabolism, the French Food Agency (AFSSA) claimed unequivocally that excess consumption of creatine and creatinine might induce formation of carcinogenic and mutagenic compounds which could put athletes and consumers of exogenous creatine at risk (Wyss and Kaddurah-Daouk 2000). (Evaluation of risks induced by creatine consumer and truth on allegations related to sport performance or increase in muscle mass http://www.afssa.fr).

It was suggested that increased conversion of creatine to sarcosine could result in the formation of cytotoxic agents such as methylamine, which is deaminated by semicarbazide-sensitive amine oxidase (SSAO, EC 1.4.3.6) to produce formaldehyde and hydrogen peroxide (Fig. 3).

Methylamine and formaldehyde are known to be potential cytotoxic agents and can be demonstrated by urine analyses (Yu and Zuo 1996; Deng et al. 1998; Mitchell and Zhang 2001; Yu et al. 2003). Formaldehyde has the potential to cross-link proteins and DNA, leading to cytotoxicity and carcinogenic effects in cells (Headlam et al. 2000; Quievryn and Zhitkovich 2000). The toxic aldehyde is related to different pathological conditions such as vascular damage, diabetic complications, and nephropathies.

Yu and Deng (2000) administered a single dose of creatine (50 mg/kg) to mice but this did not seem to alter the urinary methylamine and formaldehyde excretion. However, indirect selective inhibition of SSAO activity dramatically induced a fivefold increase in methylamine and formaldehyde excretion. The authors concluded that chronic administration of a large quantity of creatine can increase the production of formaldehyde, which may potentially cause serious unwanted side-effects on healthy men. This conclusion was amplified by the AFSSA, which banned the buying of creatine.

An early German publication showed that exercise (one man undertaking a strenuous ski race) induced a 2.5-fold increase in the urinary excretion of methylamine (Kapeller-Adler and Toda 1932). The authors argued that all conditions associated with creatinuria (such as supplementation or muscular exertion) would result in an increased

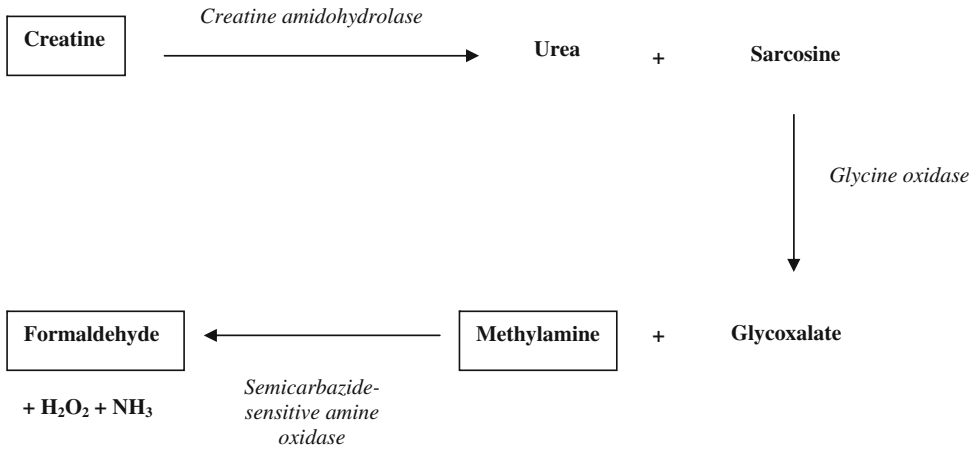

Fig. 3 Synthesis of methylamine and formaldehyde from creatine in human subjects

excretion of methylamine. However, the authors collected only an aliquot of urine after exertion, and did not provide any information on urine output itself.

Recently, we investigated 20 male young healthy subjects who were supplemented daily with 21 g creatine monohydrate for 2 weeks (Poortmans et al. 2005). Urine was collected for 24 h, before and after creatine supplementation for determination of creatine, creatinine, methylamine, formate and formaldehyde. With creatine supplementation, 24-h urinary output of methylamine and formaldehyde increased 9.2- and 4.5-fold, respectively, ($P < 0.001$) with no increase in formate excretion (Fig. 4).

Following creatine feeding, there was no correlation between plasma creatine and urine methylamine ($r^2 = 0.025$, $P =$ NS) or formaldehyde ($r^2 = 0.017$, $P =$ NS). The results were confirmed by another study looking at urine methylamine determination after exogenous creatine supplementation (Sale et al. 2009), although in this case lowering the peak in the plasma creatine concentration, by spreading the dose evenly throughout the day, markedly lowered the urinary output of methylamine.

These investigations indicate that short-term oral creatine feeding in healthy subjects enhances the mechanisms leading to the conversion of creatine to sarcosine and then to methylamine, the latter giving rise to formaldehyde. In turn the conversion of formaldehyde to formate should be rather rapid in cells (Boeniger 1987). Using both rat and mice models, it was shown that in vivo deamination of methylamine produce formaldehyde and hydrogen peroxide, both of which are recognized as cytotoxic substances (Deng et al. 1998; Yu and Deng 2000). Consequently, these authors 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 in renal glomerula (Deng et al. 1998; Yu and Deng 2000). Our results support this hypothesis in humans (Poortmans et al. 2005; Sale et al. 2009).

The results of our studies suggest an increase in the conversion of creatine to sarcosine, and subsequently to methylamine following creatine monohydrate supplementation. As compared to basal state (0.40–0.70 mg/day), methylamine reached a mean value of 5.00–7.00 mg/24 h after 5–14 days of exogenous creatine. These levels did not reach the normal upper limit values from healthy humans, up to 35 mg/day (mean + 3SD) (Mitchell and Zhang

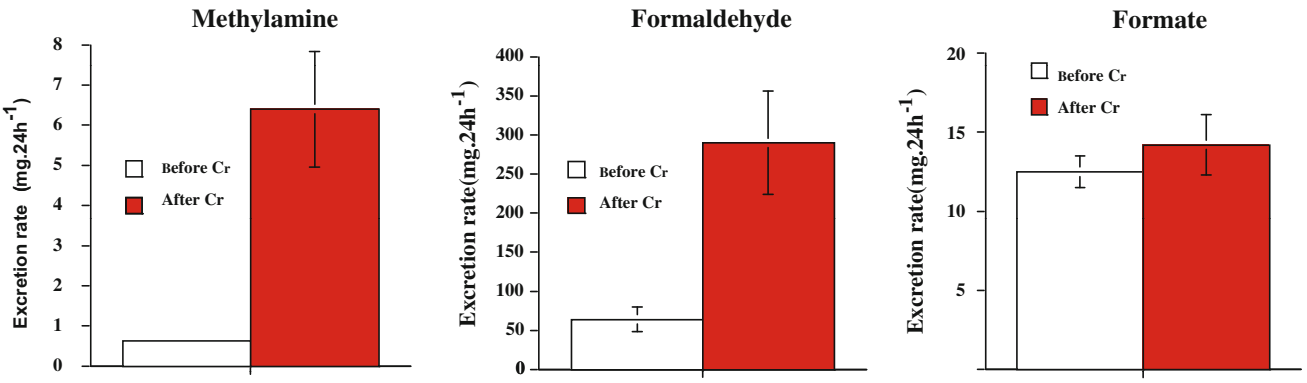

Fig. 4 Urine excretion of methylamine, formaldehyde and formate after 2 weeks of creatine monohydrate supplementation (21 g/day). After Poortmans et al. (2005)

2001). Similarly, despite a 4.5-fold increase (mean 0.29 mg/day, vs. 0.06 under basal state) the urine formate remained below the upper range (14–20 mg/day) reported in healthy subjects (Schmidt 1967; Berode et al. 2000; Kage et al. 2004).

As creatine may be transformed to sarcosine by microbial enzymatic reactions (Wyss and Kaddurah-Daouk 2000), it is likely that some methylamine is formed in the intestine with the potential to damage the integrity of the intestinal epithelium. Methylamine is toxic to human endothelial cells and forms patch-like lesions (Yu et al. 2003) and even kidney damage (Yu and Zuo 1996). In mammals, SSAO activity has been found in various tissues associated with the vascular system (Garpenstrand et al. 2004; Kinemuchi et al. 2004). Therefore, it is likely that the deamination of any methylamine formed in the intestine occurs in the circulation. It could also be speculated that any increase in methylamine in blood, in the presence of SSAO, might lead to formation of formaldehyde leading to microangiopathy in the renal glomeruli (Yu et al. 2003; Kinemuchi et al. 2004).

Even if systematic deleterious effects are not observed, it cannot not be excluded that a systematic production of low doses of cytotoxic agents never induces any incidences of nephropathy. Clearly, epidemiological data are required to evaluate potential risks over a larger cohort of individuals. In terms of the results of the present investigation, caution should be applied. Kidney function of patients and healthy subjects supplemented with creatine on a regular basis should be monitored throughout the ingestion period.

To conclude, our investigations showed that short-term and heavy load of oral creatine supplementation (up to 21 g/day) stimulates the production of an excess of methylamine and formaldehyde in urine of healthy humans. This may be reduced by spreading the creatine load more evenly throughout the day or through the use of an appropriate slow release formulation (Sale et al. 2009). 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.

Induction of carcinogenic and mutagenic amino-imidazo-azaarene formation

The processing of foods, in particular frying and broiling of meat, is associated with the generation of mutagenic and carcinogenic substances, namely the amino-imidazo-azaarenes products referred to as “heterocyclic amines (HCA)” for simplicity (Wyss and Kaddurah-Daouk 2000). The formation of HCA has been shown to require three classes of precursors: creatine/creatinine, free amino acids, and sugar (Skog et al. 1995). Formation of HCA, which are classified into five groups (see Wyss and Kaddurah-Daouk for details) (Fig. 5), is further dependent up on the cooking time and temperature (over 250°C) (Knize et al. 1999; Gooderham et al. 2001). Maximal mutagen yield is achieved by mixing creatine or creatinine with an amino acid and a sugar with a molar ratio of 1:1:0.5 (Wyss and Kaddurah-Daouk 2000; Heddle et al. 2001). Creatinine rather than creatine is likely to be the actual precursor of the HCA mutagens (Wyss and Kaddurah-Daouk 2000). Among the HCA compounds, IQ (Imidazo-quinoxaline), 8-MeIQx (8-methyl-imidazo-quinoxaline), 4, 8-DiMeIQx (4,8-dimethyl-imidazo-quinoxaline) and PhIP (Imidazo-pyridine) are the most important mutagens and together contribute about 80% of the mutagenicity. HCA are formed at high temperatures during frying or broiling of meat (barbecue effect), but it is questionable whether they represent any significant cancer risk. Formation of HCA from creatine or creatinine at 37°C is unlikely to occur and therefore can be discounted as a significant cancer risk with oral creatine supplementation (Wyss and Kaddurah-Daouk 2000).

Based on current knowledge, the probability that nitrosation products of creatine are formed in the stomach to any significant extent is close to zero (Wyss and Schulze 2002). A short publication by Derave et al. (2006) supports

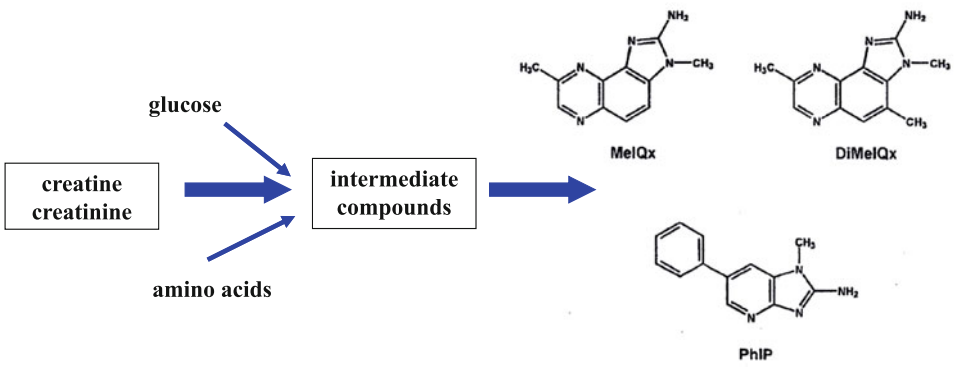

Fig. 5 General scheme of the synthesis of heterocyclic amines from creatine/creatinine, glucose and several free amino acids by intestinal bacteria or heating these compounds over 250°C (see text)

this conclusion. These authors investigated in a double-blind, placebo-controlled study the urinary excretion of *N*-nitrososarcosine after 1-week high-dose (20 g/day) and 20-week low-dose (5 g/day) creatine supplementation in healthy humans. They concluded that creatine ingestion does not increase the urinary excretion of the carcinogen *N*-nitrososarcosine.

The identification of HCA in human urine is not an easy procedure. The analytical methods involve solid-phase extraction and quantification by combined liquid chromatography-tandem mass spectrometry to identify the major HCA in urine (Friesen et al. 2001; Knize et al. 2001, 2002). Nevertheless, one will have to quantify this potential hypothetic risk to definitively exclude what is an unproved allegation, but one which is often cited in non-scientific publication and the media.

Advice and practical conclusions

The purpose of this review was presenting data and conclusions on the potential harmful effects of oral creatine supplementation in healthy individuals. Despite papers and editorials published in scientific and sports media, there are no real incidents of muscle cramps, gastrointestinal discomfort, muscle fibre rupture, liver and kidney impairment after regular supplementation with creatine. The few renal incidents that have been reported remain largely anecdotal. Even if there are no obvious health risks associated with oral creatine supplementation it may be best to err on the side of caution when supplementing on a chronic basis. Excess creatine ingestion is still a burden to be eliminated by the kidney. Regular checkups should be the elementary tactic with annual investigation of blood levels of liver enzymes, urea, and creatinine. The analysis of the urinary albumin excretion rate (<20 μg/min or <20 μg albumin/mg creatinine) appears to be the simplest, less expensive, most accurate test to assess early incident of kidney impairment. Should the normal range be exceeded under resting condition, i.e. after 20 h of physical activity, further investigations should be undertaken by a specialist in nephrology (Poortmans and Francaux 2002).

Eventually, we advise that high-dose creatine supplementation should not be used by anyone with pre-existing renal disease or those with a potential risk for renal dysfunction (diabetes, hypertension, reduced glomerular filtration rate). Great care should also be taken as far as the purity of exogenous creatine supplements is concerned. Analytical tests must provide evidence that unique nutraceutical compositions and preparations are assuredly safe and free from contaminations.

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