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Adverse Effects of Creatine Supplementation

Fact or Fiction?

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Abstract

The consumption of oral creatine monohydrate has become increasingly common among professional and amateur athletes. Despite numerous publications on the ergogenic effects of this naturally occurring substance, there is little information on the possible adverse effects of this supplement. The objectives of this review are to identify the scientific facts and contrast them with reports in the news media, which have repeatedly emphasised the health risks of creatine supplementation and do not hesitate to draw broad conclusions from individual case reports.

Exogenous creatine supplements are often consumed by athletes in amounts of up to 20 g/day for a few days, followed by 1 to 10 g/day for weeks, months and even years. Usually, consumers do not report any adverse effects, but body mass increases. There are few reports that creatine supplementation has protective effects in heart, muscle and neurological diseases. Gastrointestinal disturbances and muscle cramps have been reported occasionally in healthy individuals, but the effects are anecdotal. Liver and kidney dysfunction have also been suggested on the basis of small changes in markers of organ function and of occasional case reports, but well controlled studies on the adverse effects of exogenous creatine supplementation are almost nonexistent.

We have investigated liver changes during medium term (4 weeks) creatine supplementation in young athletes. None showed any evidence of dysfunction on the basis of serum enzymes and urea production. Short term (5 days), medium term (9 weeks) and long term (up to 5 years) oral creatine supplementation has been studied in small cohorts of athletes whose kidney function was monitored by clearance methods and urine protein excretion rate. We did not find any adverse effects on renal function.

The present review is not intended to reach conclusions on the effect of creatine supplementation on sport performance, but we believe that there is no evidence for deleterious effects in healthy individuals. Nevertheless, idiosyncratic effects may occur when large amounts of an exogenous substance containing an amino group are consumed, with the consequent increased load on the liver and kidneys. Regular monitoring is compulsory to avoid any abnormal reactions during oral creatine supplementation.

For the last 7 years, top athletes first, then sport professionals and amateur sports participants have been using oral creatine supplementation on a regular basis as an ergogenic aid to improve performance. The amount taken of this supplement ranges from a few grams to tens of grams per day for weeks, months or even years. Several reviews have been devoted to the subject, focusing attention on the benefits for performance.[1-9] A recent book by Williams et al.[10] is a highly comprehensive manual for creatine consumers, providing numerous insights on this naturally occurring substance.

On the contrary, there is little information about the adverse effects of creatine supplementation.[11,12] These authors discussed mainly hypothetical effects arising from a small number of scientific publications. Besides this, there has been much invalid information published by newspapers and periodicals. The aim of the present review is to shed light on the facts and to reject several allegations supported by no scientific evidence. Recommendations will be proposed to minimise any health problems arising from creatine supplementation.

1. The Consumers of Creatine

According to the French newspaper *Le Monde*,[13] the American sport community has been under a 'creatine supplement spell'. Up to 75% of the San Francisco 49ers and the Denver Broncos football players are regular consumers of oral creatine. Schneider reported that US Navy Seals (special forces) use several nutritional supplements to increase muscle mass and that creatine is one of the most commonly used supplements.[14] Williams et al.[10] also revealed that over 90% of weightlifters and bodybuilders in the US are regular users of creatine monohydrate. They are male, with an average age of 32 years, have attended or graduated from college and have a substantial income.

The British newspaper *The Independent* surveyed British sportsmen and -women using creatine as an ergogenic aid.[15] More than 360 elite competitors responded to the questionnaire. Nearly 57% had tried creatine and 44% reported using it on a regular basis. Among them were Linford Christie (sprinter, gold medal at the 1992 Barcelona Olympics) and Mark Foster (swimmer, gold medal at the 1998 Commonwealth Games). Among rugby league players and weightlifters, the figure was 100%. However, a number of coaches in Australia and New Zealand who once recommended creatine to their players have stopped doing so for the simple reason that not nearly enough is known about the long term consequences of using it. The British Olympic Association refuses to endorse the substance because of fears over long term effects.

The US Food and Drug Administration (FDA),[13] the Association of Professional Team Physicians[13] and the American College of Sports Medicine[16] concluded that while short term studies look positive for oral creatine supplementation, much more long term research needs to be done before one can issue a verdict on its health status. In doubt, individuals should be left to their free choice and interpretation. However, the medical commission of the International Olympic Committee has decided that creatine is not a prohibited drug but a food supplement; its chairman, Prins Alexandre de Merode, concluded ironically by saying that 'It is like eggs and foie gras, if you take too much you are sick!'. Quite surprisingly, the French Government has decided not to decide. Indeed, a commission of the Ministry of Youth and Sports pointed out that creatine has no legal right to be sold in France. Thus the product cannot be bought on the market nor in pharmacies, and the government does not need to provide any legal judgement on creatine. Meanwhile, they advise against its use.

2. Allegations From the Media

Concern about the deleterious consequences of oral creatine supplementation was initiated in early 1998 when Pritchard and Kalra,[17] 2 British nephrologists, published a paper in *The Lancet* suggesting that there was 'strong circumstantial evidence that creatine was responsible for the deterioration in renal function.' The 25-year-old man mentioned in this study had presented 8 years previously with focal segmental glomerulosclerosis and frequently relapsing corticosteroid-responsive nephrotic syn-

drome. He had required treatment with cyclosporin, an immunosuppressive drug well known for its nephrotoxicity, for the last 5 years to minimise nephrotic relapses. This man began creatine supplementation for soccer training in mid-August 1997 with a loading dosage of 5g three times daily for 1 week, followed by a maintenance dosage of 2 g/day which he had been taking for 7 weeks. His glomerular filtration rate dropped by 50% but returned to normal values 1 month after stopping the supplements.

Just 3 days after this publication, the French sports newspaper *L'Equipe*[18] reported that creatine is dangerous for the kidneys in any condition. This 'news' was taken up by several European newspapers.[13,19-21] Creatine became the 'champion's Viagra', inducing renal impairment, liver alterations and even death. Indeed, Pritchard and Kalra[17] commented on the cases of 3 American college wrestlers who died. However, we now know from the police investigation that those people did not die from creatine supplements (E. Zambraski, personal communication).

A web site of the FDA[22] gives regular reports of complaints from voluntary consumers of 'nutritionals' or from healthcare professionals. A search of the most recent report (20 October 1998) revealed 32 matches for creatine. The problems reported include dyspnoea, fatigue, grand mal seizure, intracerebral haemorrhage, vomiting, diarrhoea, nervousness and anxiety, polymyositis, myopathy, rhabdomyolysis, severe stomach cramps, deep vein thromboses, atrial fibrillation, cardiac arrhythmia, chest pain and death. Meanwhile, the FDA asks the reader to keep in mind that 'there is no certainty that a reported adverse event can be attributed to a particular product or ingredient. The available information may not be complete enough to make this determination.' In other words, there is no scientific evidence to correlate oral creatine monohydrate supplements with any of these reported adverse effects.

3. Effects of Oral Creatine Supplementation

3.1 Body Mass

One of the effects of oral creatine supplementation regularly mentioned by consumers is an increase in body mass (BM), particularly muscle mass. On scientific grounds, the situation is less clear. Indeed, the average increase in BM reported in the literature amounts to 1 to 2kg or 1 to 2.3% of total BM (table I). However, the effects of short term (<10 days) and medium term (>10 days) supplementation on BM should be distinguished. In fact, short term supplementation is based on a mean of 20 g/day, whereas medium term supplementation generally involves consumption of 2 to 10 g/day. Table I emphasises this difference and its consequences for BM. It may be observed that 68%[23-30,32,41-47] and 70%[45,48,50-54,56,57] of the reported publications showed an increase in total BM for short and medium term supplementation, respectively. Thus, despite the reduced daily dosage of creatine supplements during medium term intake, most of the studies reported an increase in BM. Nevertheless, about 30% of published papers do not report any change in BM, either after short term[31,33-40,55] or medium term[37,39,49,55,58] supplementation.

Two possible reasons may be proposed to explain these discrepancies: the characteristics of the individuals and the supplementation protocol. Sedentary people, physically active individuals and recreational athletes seem to respond equally to oral creatine supplementation. Thus, individuals need not be physically active to increase BM after oral creatine supplementation despite different daily energy intake. Several studies on female volunteers did not show any modification in BM after creatine supplements.[33,34,36,38,55,49] Unfortunately, none of these studies controlled the menstrual cycle of the volunteers. It is currently difficult to postulate a gender dependence, since we do not have any scientific evidence to support those differences. Not all studies have been made using a control group (no training session) in addition to a placebo and creatine supplementation group. We[54] have per-

Table I. Body mass changes induced by creatine supplementation

Study	Year	Gender	Population	Dosage (g/day)	Number of days	Effect on body mass (%)
Short term (<10 days)						
Balsom et al.[23]	1993	M	Active	24	6	+1.5
Balsom et al.[24]	1993	M	Trained	20	6	+1.2
Greenhaff et al.[25]	1994	M	Active	20	5	+1.0
Stroud et al.[26]	1994	M	Active	20	5	+1.3
Balsom et al.[27]	1995	M	Active	20	6	+1.4
Dawson et al.[28]	1995	M	Active	20	5	+1.0
Green et al.[29]	1996	M	Sedentary	20	5	+1.1
Mujika et al.[30]	1996	M, F	Swimmers	20	5	+1.0
Vandenberghe et al.[31]	1996	F	Active	0.5 g/kg	6	Stable
Becque et al.[32]	1997	M	Weight lifters	20	5	+2.3
Godly & Yates[33]	1997	M, F	Cyclists	20	5	Stable
Grindstaff et al.[34]	1997	M, F	Swimmers	21	9	Stable
Hamilton-Ward et al.[35]	1997	F	Athletes	25	7	Stable
Prevost et al.[36]	1997	M, F	Students	18.8	5	Stable
Stout et al.[37]	1997	M	Football	21	5	Stable
Terrillion et al.[38]	1997	F	Runners	20	5	Stable
Vandenberghe et al.[39]	1997	F	Students	20	4	Stable
Bermon et al.[40]	1998	M, F	Active	20	5	Stable
Maganaris & Maughan[41]	1998	M	Active	11.4	5	+2.3
Oöpik et al.[42]	1998	M	Karatekas	20	5	+1.3
Snow et al.[43]	1998	M	Active	30	5	+1.3
Robinson et al.[44]	1999	M	Active	20	5	+1.4
Volek et al.[45]	1999	M	Trained	25	7	+2.1
Oöpik et al.[46]	1999	M	Wrestlers	20	5	+1.3
Urbanski et al.[47]	1999	M	Active	20	5	+1.0
Medium term (>10 days)						
Earnest et al.[48]	1995	M	Weight lifters	20	14	+1.9
Thompson et al.[49]	1996	F	Swimmers	2	42	Stable
Goldberg & Bechtel[50]	1997	M	Football	3	14	+0.8
Kirksey et al.[51]	1997	M, F	Athletes	0.3 g/kg	42	+2.0
Stout et al.[37]	1997	M	Football	10.5	51	Stable
Vandenberghe et al.[39]	1997	F	Students	5	60	Stable
Volek et al.[52]	1997	M	Trained	3	47	+1.8
Bermon et al.[40]	1998	M, F	Active	3	47	Stable
Kreider et al.[53]	1998	M	Football	16	28	+1.0
Francaux & Poortmans[54]	1999	M	Active	3	63	+2.9
Leenders et al.[55]	1999	M, F	Swimmers	10	14	Stable
Stone et al.[56]	1999	M	Football	8	35	+1.4
Volek et al.[45]	1999	M	Trained	5	77	+6.3
Rawson et al.[57]	1999	M	Old	20	30	+0.6
Francaux et al.[58]	2000	M	Active	21	14	Stable

formed such a comparison in order to be certain that the increase in muscle mass could not be attributed to the effect of training itself (table II). No statistically significant differences in BM were observed in control individuals followed during 9 weeks compared with active people involved in re-

sistance training for the same period of time. On the contrary, the creatine supplementation group had an increased BM.

The increase in BM could be attributed to the carbohydrate supplements that were added to the creatine ingestion in several studies. Indeed, water binding to muscle and liver glycogen occurs after glucose loading. Green et al.[29,59] and Robinson et al.[44] observed that whole body and muscle creatine retention was increased when large amounts of simple carbohydrates were ingested in conjunction with creatine. However, the conclusions of the 2 studies are not similar. Green et al.[59] reported that creatine loading (20 g/day for 5 days) increased BM by 0.6kg, but when 370g of glucose was added over the course of each day of the study the volunteers gained an additional 1.5kg. On the contrary, Robinson et al.[44] did not observe significant BM change after 5 days of glucose supplementation at 277 g/day, but did report a 1.4% increase (1.0kg) after supplementation with creatine + carbohydrate.

It has been demonstrated that supraphysiological circulating concentrations of insulin, as induced by glucose ingestion, are required to augment muscle creatine accumulation in humans.[60] Consistent with this observation, Willott et al.[61] reported that the highly insulin-sensitive rat soleus muscle had higher rates of creatine uptake than the relatively less insulin-sensitive extensor digitorum longus (EDL) muscle. However, the same authors pointed out that insulin had no direct effect on [^{14}C]-labelled creatine uptake rates at concentrations for which effects are seen on glucose uptake, glycogen synthesis and glycolysis. Moreover, using a competitive inhibitor (β-guanidopropionic acid) of creatine uptake and low extracellular Na^+ concentrations to study the rate of [^{14}C]-labelled creatine uptake in isolated rat muscle, Willott et al.[61] suggested that the rate of creatine uptake is strongly dependent on the extracellular Na^+ concentration, insulin playing only a minor role in the regulation of creatine transfer. Thus, the mechanisms involved in the control of creatine accumulation in skeletal muscles still need to be investigated.

The increase in BM after creatine supplementation has been attributed to fat-free mass.[32,48,51] Nevertheless, this increase in muscle tissue may be due to water retention in the intracellular compartment or to an increase in dry mass. Hultman et al.[62] suggested that the increase in BM during short term creatine feeding is likely to be attributable to body water retention, since they observed a 0.6L decline in urinary volume after ingestion of creatine 20 g/day for 6 days. Furthermore, Ziegenfuss et al.[63] reported a 6.6% increase in thigh skeletal muscle volume and a 2 to 3% increase in total body and intracellular water volume in aerobic and cross-trained men after short term oral creatine feeding. Recently we measured the incorporation of intra- and extracellular water (by bio-impedance) in volunteers receiving creatine supplementation over a period of 9 weeks (table II).[54] The observed increase in BM (2kg) could be attributed partially (55%) to an increase in the body water content and more specifically to an increase in the volume of the intracellular compartment. Nevertheless, the relative volumes of the body water compartments remained constant, and therefore the gain in BM cannot be attributed to water retention, but probably to dry matter growth

Table II. Effect of 9 weeks of creatine supplementation on body composition estimated by bio-impedance in trained volunteers. Values are means ± SD (after Francaux and Poortmans[54])

Variable	Placebo group		Creatine group	
	day 0	day 63	day 0	day 63
Body mass (kg)	71.9 ± 7.3	72.6 ± 6.7	69.8 ± 8.9	71.8 ± 9.0*
Total body water (kg)	39.6 ± 2.5	40.1 ± 2.2	38.0 ± 3.9	39.1 ± 4.1*
Extracellular water (%)	25.9 ± 1.3	26.1 ± 2.0	25.4 ± 1.3	25.5 ± 1.3
Intracellular water (%)	29.5 ± 1.2	29.3 ± 1.3	29.2 ± 1.2	29.3 ± 0.9

* Significantly different ($p < 0.05$) between placebo group and creatine supplementation when comparing the changes between 0 and 63 days.

accompanied by the normal increase in water volume.

The hypothesis of a dry mass increase during creatine supplementation was introduced in 1972 by Ingwall et al.[64] from *in vitro* experiments on mononucleated muscle cells from breast muscle from 12-day chick embryos. Their experiment demonstrated that skeletal muscle cells formed either *in vitro* or *in vivo* synthesise myosin heavy chain faster when supplied with creatine *in vitro*. The response was apparent within 4 hours after addition of creatine to the culture medium and was concentration dependent over the range of 10 to 100 %mol/L (1.3 to 13 mg/L). Two years later, Ingwall et al.[65] showed that, in cultures of differentiating skeletal muscle, creatine stimulated selectively the rate of synthesis, and not the rate of degradation, of the 2 contractile proteins actin and myosin heavy chain. The same group extended their previous research to isolated hearts from 17- to 21-day fetal mice maintained in organ culture.[66]

More recently, Bessman and Savabi[67] suggested that creatine could induce muscle hypertrophy in adults. They founded their hypothesis on the increased uptake of amino acids by the muscle and thereafter an enhanced biosynthesis of myofibrillar proteins. However, they stated that the concentration of creatine *per se* might not be responsible for the stimulation of protein synthesis seen in physiologically active muscle. It might well be the increased transport of phosphorylcreatine in the intervening space during contraction that makes more energy available for the ribosomes.

Flisinska-Bojanowska[68] conducted an experiment on rats supplemented with creatine (10 mg/day/100g bodyweight). She electrostimulated (50Hz, 10 min/day for 14 days) the gastrocnemius muscle, and fragments of the white and red portions of the muscle were analysed for soluble and myofibrillar proteins. The creatine-supplemented rats had a 16% increase in myofibrillar proteins, specifically in the white portion of the gastrocnemius, when compared with the control group (no creatine, no stimulation). However, when rats were electrostimulated without creatine supplementation, the increase in myofibrillar proteins amounted to 50% in the white portion and 37% in the red portion of the muscle. Creatine supplementation alone did not change the content of the white muscle but increased the myofibrillar proteins in white muscle by 18%. Consequently, these results do not establish a clear beneficial effect of creatine supplements on muscle proteins.

Two further studies support neither the conclusion of Ingwall et al.[65] and Flisinska-Bojanowska,[68] nor the hypothesis of Bessman and Savabi.[67] Brannon et al.[69] investigated the combined effects of creatine supplementation (3.3 mg/g of chow diet) and high intensity run training on the performance capacity and biochemical properties of rodent skeletal muscle. There were no significant changes in either phosphorylcreatine kinase activity or myosin heavy chain isoform distribution following training or supplementation. However, these authors did not give any data on the synthesis of myosin. Fry and Morales[70] reexamined the effects of creatine supplementation on muscle protein synthesis in tissue culture. They could not support the observation of Ingwall et al.[65]

On the contrary, it seems that when rats are depleted of creatine through administration of the analog β-guanidopropionic acid, there is a reduction of muscle myofibrillar proteins and atrophy of fibre II.[71,72] Adam et al.[73,74] investigated running performance and myosin isomers after β-guanidopropionic acid treatment. The drug did not induce any change in running performance, but the myosin isomers appear to be reoriented towards the type I phenotype.

To conclude, there is as yet no evidence that creatine supplementation induces muscle protein synthesis *in vivo*. Experimental protocols are lacking in humans.

Finally, athletes in some disciplines (wrestling, judo, weightlifting, karate, etc.) try to lose BM to compete at an optimal condition below their usual BM. Ööpik et al.[42] asked karate practitioners to reduce their BM by 5% over 5 days while ingesting 20g creatine monohydrate per day during the same period. The creatine group had a smaller reduction

in BM (–3.3%) compared with the placebo group (–4.3%). Thus, the investigators suggested that the differences in the extent of BM reduction may have been caused by the effect of creatine on this variable. However, there was already an initial difference in BM between the 2 groups, the creatine groups being lighter by 1.7kg. This difference might interfere with the restriction protocol to an unknown extent.

3.2 Muscle Cramps

Anecdotal reports from athletes have claimed that creatine supplementation may induce muscle cramps (see the FDA web site[22]). In a recent unpublished study, we investigated 12 young, healthy, physically active males who received creatine 3 g/day over a period of 28 days. Five athletes experienced at least 1 cramp during sporting activities over the supplementation period (there was no history of cramp for any of these athletes before supplementation). Nevertheless, we have no proof that these cramps are directly related to the creatine supplementation.

The prevalent hypothesis to explain this potential adverse effect was an imbalance in muscle electrolytes. However, Kreider et al.[53] investigated athletes involved in heavy resistance training (5 hours/day) for 28 days. They were supplemented daily with 15.75g of creatine monohydrate. There was no evidence of muscular cramping during resistance training sessions or during performance trials. Along the same lines, Vandenberghe et al.[39] studied sedentary female volunteers who took part in 10 weeks of resistance training with creatine supplementation (20 g/day for 4 days, then 5 g/day up to 10 weeks). No spontaneous adverse effects were reported during the entire duration of the study. Nevertheless, Juhn et al.[75] recently reported muscle cramping in 25% of 52 baseball and football players who were supplemented with 6 to 8 g/day during 5 (baseball) and 3 (football) months.

The anecdotal reports of muscle cramping might be due to the intensity of exercise rather than creatine supplementation. Staying well hydrated could reduce this risk. Moreover, psychological stimulation could cause an individual to exercise over his/her optimal intensity. Further epidemiological studies should be performed to evaluate this potential adverse effect.

3.3 Gastrointestinal Complaints

Even if there are anecdotal reports of gastrointestinal distress (stomach upset, vomiting, diarrhoea) among consumers of oral creatine, these assertions are not supported by real evidence. The scientific literature lacks precise information on this matter. Nevertheless, one report from Vandenberghe et al.[39] stated that one-third of their volunteers (3 of 9) had minor gastrointestinal distress during 3 days of creatine (40 g/day) and caffeine (400 mg/day) supplementation. Also, Juhn et al.[75] reported diarrhoea in 31% of their baseball and football players who were supplemented with 6 to 8g of creatine monohydrate during 5 (baseball) and 3 (football) months. They suggested that this adverse effect may be the result of the unusually high osmotic load imposed on the digestive tract of some study participants. On the contrary, Kreider et al.[53] did not observe any gastrointestinal disturbances among participants in their study of 15.75 g/day. Greenhaff[76] supported this observation in a population ingesting 20 g/day. However, he mentioned that some discomfort can occur if creatine is incompletely dissolved before ingestion.

In conclusion, there is no reason to believe that oral creatine supplementation has any detrimental effect on the gastrointestinal tract.

4. Beneficial Effects in Health and Disease

As well as athletes searching for increased performance, there are individuals who take oral creatine supplements in order to counteract the effects of aging or specific pathological conditions.

4.1 Healthy Individuals

Tissue uptake of creatine into muscles and brain is accomplished by a specific creatine transporter.[77] A recent investigation by Dechent et al.[78] exam-

ined the extent of cerebral metabolite alterations induced in humans after a single dose (20g) of creatine monohydrate as well as in response to medium term administration (20 g/day) over a period of 4 weeks. The results showed 8.7% increase of total creatine across whole brain areas, with a more specific pronounced effect in the white matter (+11.5%) and thalamus (+14.6%) and no change in water concentration. The oral administration of creatine appears to maintain cellular integrity and normal brain function.

Aging decreases muscle mass, strength and exercise performance.[79] Rawson et al.[80] demonstrated that older men (aged >60 years) supplemented with creatine for 5 days had a slight increase (+0.5kg) in BM, but the increase was still smaller than has been shown to occur in younger individuals. There was a further increase in BM to +0.78kg with creatine supplementation for 30 days.[57] However, there were no statistical differences versus a placebo group who received the same amount of additional carbohydrate load (100 g/day). Nevertheless, the creatine-supplemented group had reduced muscle fatigue.

Bermon et al.[40] followed men and women aged 67 to 80 years who were supplemented with oral creatine monohydrate for 52 days. Some volunteers also underwent strength training for 7 weeks. The results did not show any benefits from oral creatine supplementation in terms of body composition and maximal dynamic strength in the elderly compared with a control group.

However, Smith et al.[81] investigated the effects of creatine supplementation and age on muscle phosphorylcreatine metabolism and performance by using ^{31}P-magnetic resonance spectroscopy. They compared middle-aged (>50 years) and young (<40 years) volunteers consuming 20 to 25g of creatine monohydrate daily for 5 days. Both groups performed a single-leg knee extension exercise. Before the creatine load, the older volunteers had a lower resting muscle phosphorylcreatine concentration compared with the younger volunteers. After exercise, the initial phosphorylcreatine resynthesis was slower in the middle-aged group. After creatine supplementation, resting phosphorylcreatine increased more in the elderly group than the younger group, eliminating the difference in resting muscle observed before the supplementation. Moreover, the phosphorylcreatine resynthesis was increased to a rate similar to that of the younger group after creatine supplementation. Thus, this study indicated that middle-aged individuals had greater improvements in muscle phosphorylcreatine availability, phosphorylcreatine hydrolysis during exercise and initial resynthesis after creatine supplementation.

It seems clear that further studies are needed to validate any beneficial effects of creatine supplements in the elderly.

4.2 Disease States

A few studies have evaluated the benefit of oral creatine supplementation in some pathological conditions. The aim was to provide additional energy stores as phosphorylcreatine to compensate for exertional fatigue and creatine deficit in humans and animals.

4.2.1 Heart Disease

Since total creatine content is at least 20% lower in the diseased human heart, Gordon et al.[82] supplemented patients with chronic heart disease with creatine 20 g/day for 10 days. Before and on the last day of supplementation, the patients underwent exercise on a cycle ergometer. Skeletal muscle biopsies were taken on both occasions. The creatine supplementation did not modify the ejection fraction but increased skeletal muscle phosphorylcreatine and performance as regards both strength and endurance. Andrews et al.[83] extended this previous study to male patients with stable chronic heart failure of at least 3 months duration. The patients received creatine 20 g/day for 5 days. Blood analyses (lactate and ammonium) were assayed before and after creatine supplementation (including a placebo group). The patients exercised the dominant forearm using a hand grip dynamometer (volitional exhaustion at 75% of maximum voluntary contraction). It was observed that creatine supplementation augmented skeletal muscle endurance and attenuated the release of ammonia and lactate in blood.

4.2.2 Muscle Dystrophies

Fatigue in patients with mitochondrial cytopathies is associated with decreased basal and postactivity muscle phosphorylcreatine. Tarnopolsky et al.[84] supplemented 7 of these patients with creatine (5 g/day for 14 days, then 2 g/day for 7 days). They concluded that creatine supplementation increased the strength of high intensity anaerobic and aerobic type activities in patients with mitochondrial cytopathies but had no apparent effects upon lower intensity aerobic activities.

A recent paper by Pulido et al.[85] extended this previous report to a study of Duchenne muscular dystrophy patients and *mdx* mice. Indeed, it has been reported that human and murine dystrophic muscles have decreased phosphorylcreatine and impaired Ca^{2+} regulation relative to a control group.[86] Primary cell cultures of skeletal cells from normal and *mdx* mice were incubated with creatine (20 mmol/L) for 9 to 11 days. The investigators reported that creatine supplementation enhanced myotube formation and survival when these cells are exposed to high extracellular Ca^{2+} concentration or hypo-osmotic stresses. Based on these observations, Pulido et al.[85] proposed that creatine is a substance with potential therapeutic properties in patients with neuromuscular diseases.

Gyrate atrophy of the choroid and retina is a disease characterised by progressive constriction of visual fields. Atrophy of type II muscle fibres and lower creatine content progress concomitantly with the eye disease. Therefore, Sipilä et al.[87] supplemented patients with creatine 1.5 g/day for a year. The diameters of type II muscle fibres increased by 46% and the visual-field tests showed no further constriction during the therapy.

4.2.3 Neurological Disorders

Excess oral creatine supplementation reaches both muscles and brain, and it has been proposed that creatine may be linked to neuroprotection.

Matthews et al.[88] analysed the role of creatine in Huntington's disease, which involves defects in energy production. They used rats administered 3-nitroproprionic acid to mimic Huntington's disease (intrastriatal inhibition of succinate dehydrogenase). Oral supplementation with 1% creatine dramatically reduced the striatal lesions. The authors are convinced that creatine supplementation may represent a novel therapeutic strategy for neurodegenerative diseases. The same group investigated a transgenic mouse model of amyotrophic lateral sclerosis.[89] The oral administration of 1% creatine in their daily diet improved the survival of the animals (means of 144 *vs* 157 days). Moreover, there was a complete neuroprotection of the neurons in the ventral horn of the supplemented mice as compared with 49% neuronal loss in the control mice. The therapeutic benefit of creatine on survival and motor function of induced amyotrophic lateral sclerosis appeared evident.

Proton magnetic resonance spectroscopy has been used to investigate the effects of oral creatine supplementation in rats with ischaemic events.[90] The animals were supplemented with 2.6g of creatine monohydrate/kg bodyweight per day for 10 days. Despite this huge supplementation, the rats had almost identical dynamics of cerebral lactate and glucose concentrations, even during induced ischaemia. Apparently the elevation of creatine in the brain did not rule out its neuroprotective potential. A similar study was conducted by the same group looking at brain water diffusion in creatine-supplemented rats during transient global ischaemia.[91] They reported a less severe total reduction in apparent diffusion coefficient in creatine-fed rats compared with controls. Hypoxic stress induces a reduction in water diffusion coefficient leading to tissue damage.

Creatine treatment was also applied to a patient with MELAS (myopathy, encephalopathy, lactic acidosis and stroke-like episodes).[92] After 2 weeks of creatine 10 g/day followed by 4 g/day thereafter, the patient reported reduced headache, less weakness and improved work performance.[93] When a child with an inborn error of creatine biosynthesis and total absence of brain creatine was supplemented with oral creatine 400 mg/kg/day,[94,95] the clinical symptoms were markedly attenuated, with a rise of cerebral total creatine of about 50% of the normal value.

Table III. Effects of creatinine supplementation on serum urea and liver enzymes

Variable	Baseline	Creatine	Dosage (g/day)	Duration (weeks)	Reference
Urea nitrogen (mg/dl)					
	15.8 ± 0.7	13.8 ± 1.0	10	12	Earnest et al.[96]
	15.2 ± 0.1	15.1 ± 0.8	3	9	Poortmans & Francaux[a]
		14.7 ± 0.9	<10	8-260	Poortmans & Francaux[a]
Enzymes (IU/L)					
AST	42.8 ± 22.6	35.7 ± 10.7	3	4	Poortmans & Francaux[a]
	21.3 ± 1.4	22.0 ± 1.2	10	12	Almada et al.[97]
	19.6 ± 3.7	19.1 ± 1.6	3	9	Poortmans & Francaux[a]
	23.1 ± 8.6	26.9 ± 13.0	15.75	8	Kreider et al.[53]
ALT	29.3 ± 15.4	27.0 ± 8.8	3	4	Poortmans & Francaux[a]
	65.8 ± 3.9	70.7 ± 3.7	10	12	Almada et al.[97]
	21.6 ± 2.7	18.7 ± 2.9	3	9	Poortmans & Francaux[a]
	24.1 ± 4.7	28.1 ± 9.8	15.75	8	Kreider et al.[53]
GGT	19.5 ± 5	19.8 ± 7	3	4	Poortmans & Francaux[a]
	24.7 ± 2.8	20.1 ± 1.8	10	12	Almada et al.[97]
	24.7 ± 13.2	25.2 ± 15.8	15.75	8	Kreider et al.[53]
ALP	81.3 ± 18.3	79.0 ± 16.7	3	4	Poortmans & Francaux[a]

a Unpublished data.

ALP = alkaline phosphatase; **ALT** = alanine aminotransferase; **AST** = aspartate aminotransferase; **GGT** = γ-glutamyl transferase; **IU** = international units.

5. Health Risks of Excess Creatine Supplementation

Excessive creatine supplementation may have adverse effects on organs that are involved in its metabolism. The liver synthesises a maximum of 2 g/day of creatine, one-tenth of the regular oral intake used over 5 days by most consumers. Liver enzymes are also indicators of several pathological conditions in liver and striated muscles. Excess creatine has to be excreted by the kidney, and this organ is involved in the homeostasis of the body. Finally, the brain takes up creatine, which could interfere with cerebral metabolism.

5.1 Liver Dysfunction

Despite the allegations published in sports newspapers and periodicals, there is little information on liver metabolism changes induced by oral creatine supplementation. Three publications have reported some data on liver function while consuming creatine supplements.[96-98] These results are summarised in table III, together with data we collected on creatine consumers.

The study of Earnest et al.[96] did not show any significant increase in serum urea and bilirubin throughout the duration of creatine supplementation (20 g/day for 5 days and 10 g/day for 51 days). However, creatine supplementation did increase serum urea by 17% in females. However, the urea levels remained within the range of a normal population. Earnest et al.[96] suggested that long term high-dosage creatine supplementation elicited minimal changes in the markers of hepatic function that were evaluated. Looking at their data and knowing that serum urea is not an accurate representative of liver function, we do not share their conclusion. Indeed, the same group investigated the levels of serum enzymes of liver origin.[97] No changes in enzyme levels were observed during the 8 weeks of supplementation.

Additional information was obtained after oral creatine supplementation in trained individuals (table III). No statistically significant differences were observed throughout the study as far as urea, alkaline phosphatase, aspartate aminotransferase,

alanine aminotransferase and γ-glutamyltransferase are concerned. Thus, there is no reason to believe that oral creatine supplementation, under the conditions stated in table III, would induce changes in liver function.

A recent report by Duarte et al.[99] indicated that mice supplemented with oral creatine (0.3 g/kg bodyweight for 6 days) had a liver protein content increased by 23%. Among the measured liver enzymes, the authors mentioned that aspartate aminotransferase decreased and alanine aminotransferase tended to increase.

In conclusion, creatine supplementation induces no real modification in liver metabolism.

5.2 Muscle Markers

Phosphorylcreatine kinase (PCK) is commonly used in clinical pathology as a marker of muscle enzyme efflux and thus muscle dysfunction. There are few contradictory reports in the literature related to this specific enzyme under creatine supplementation (table IV). Three publications did not report changes in total plasma PCK after 5 days of creatine supplementation with 20 g/day[98] or 6 g/day,[100] and after 4 to 8 weeks of 10 g/day.[97] However, the latter report showed a slight increase in plasma PCK in male volunteers. Kreider et al.[53] also reported a mild elevation in PCK after 28 days of 15.75 g/day. Nevertheless, it is difficult to get a clear picture of these mild changes in PCK levels, since the athletes were in heavy training, which might itself induce muscle enzyme efflux.

Moreover, plasma PCK exists in 3 different isoforms, namely MM for skeletal muscle, MB for heart and BB for brain. There is no report available that identifies the enzyme isoform that is released from the tissues. Most probably, the slight increase observed in a few reports could be attributed to the skeletal muscle isoform, but precise information is needed to confirm this hypothesis.

5.3 Kidney Impairment

In 1926, Chanutin investigated the fate of creatine when administered to 2 volunteers for 29 and 44 days, with a daily intake of 10 to 20g.[101] The absorption of creatine appeared to be complete. He found an increased creatinine excretion as well as significant positive nitrogen balance. Unfortunately, the excretion was measured for only 1 or 2 days after stopping the administration of creatine. Thus, the carry-over effects on creatinine excretion were not determined. Two years later, Rose et al.[102] reported that after 49 days of feeding creatine 1 g/day, 1 man and 1 woman had a 22 to 25% increase in creatinine excretion. Hyde[103] extended this study, looking at 14 individuals of varying age who received creatine 1 g/day for 4 to 10 weeks. Eight of their volunteers had increased creatinine excretion, whereas 6 did not. Subsequently, Crim et al.[104] gave creatine 0.23 g/day for 9 days and 10 g/day for 10 days, consecutively, to healthy young men. The men were trained on a treadmill (5 days a week) during the 9-day low creatine feeding. Creatinine excretion increased by 10 to 30% during creatine feeding. There was no significant increase in faecal nitrogen during the creatine-feeding period.

More recently, there have been several publications which showed an increase in creatinine excretion

Table IV. Effect of oral creatine supplementation on serum phosphorylcreatine kinase activity

Dosage (g/day)	Duration (days)	Activity (IU/L)		Reference
		baseline	creatine	
10 (M and F)	84	89.3 ± 10.2	97.8 ± 7.8	Almada et al.[97]
10 (M)	56	118.8 ± 18.6	181.3 ± 23.6*	Almada et al.[97]
20	5		No change	Mihic et al.[98]
20	5		No change	Engelhardt et al.[100]
15.75	28	239 ± 106	609 ± 365*	Kreider et al.[53]

* Significantly different ($p < 0.05$) from baseline value.

F = females; **IU** = international units; **M** = males.

Table V. Effect of creatine supplementation on urea excretion in urine

Dosage (g/day)	Duration (weeks)	Urea excretion (g/24h)		Authors
		baseline	creatine	
5	10	18.82 ± 2.27	19.94 ± 2.10	Vandenberghe et al.[39]
20	1	12.6 ± 2.84	10.33 ± 2.09	Poortmans & Francaux[a]
3	9	12.6 ± 2.84	10.83 ± 6.27	Poortmans & Francaux[a]
<10	8-260		12.3 ± 4.6	Poortmans & Francaux[a]

a Unpublished data.

when individuals were given creatine.[39,40,62,105,106] However, several authors did not observe any statistical changes in creatinine excretion after 5 days,[41,107] 9 weeks[108] or 10 weeks[39] of oral creatine supplementation in trained individuals. Urine output was also measured after creatine supplementation in some studies, and the results are contradictory: either an increase,[40] a stable output[41,108] or a decline in urinary volume.[62] Hultman et al.[62] suggested that the increase in BM during acute creatine loading is likely to be attributable to body water retention. This explanation does not follow from the other studies.

Urea output was also taken into consideration in a few studies. No modification in urea excretion rate was observed after 9 to 10 weeks and 10 months to 5 years of oral creatine supplementation (table V). Therefore, it seems reasonable to say that the liver does not seem to be overproducing urea when healthy individuals ingest creatine in excess.

Creatine at a load of 2 to 20 g/day is totally absorbed by the intestinal tract. However, skeletal muscle cannot take up all this excess creatine and creatine must be excreted in the urine. The excreted creatine represents 40 to 60% of the original load.[41,39,40,107,109]

An early report from Earnest et al.[96] stated that creatine supplementation had minimal changes in the markers of renal function. Unfortunately, they used plasma urea, which does not represent a valuable marker when taken without any urine determination to assess renal function. More troubling, their data did not show any differences in plasma urea for male volunteers and a modest increase (17%) for female volunteers.

The first real investigation (blood and urine values) on renal function during oral creatine supplementation was published in 1998 in the case report described in section 2.[17] This patient, who had pre-existing kidney disease, had taken oral creatine 15 g/day for 1 week and then a maintenance dosage of 2 g/day for 7 weeks. His renal function deteriorated, with a creatinine clearance of 54 ml/min (nor-

Table VI. Effect of oral creatine supplementation on kidney function (excretion rates and clearances)[107,108,110]

Dosage (g/day)	Duration	Baseline	Creatine
Albumin excretion (g/min)			
20	5 days	5.8 ± 0.7	6.9 ± 0.9
3	9 weeks	5.8 ± 0.7	9.0 ± 1.5
<10	8 weeks-5 years		6.3 ± 1.1
Creatine clearance (ml/min)			
20	5 days	3.8 ± 2.5	210 ± 108*
3	9 weeks	3.8 ± 2.5	59 ± 18*
<10	8 weeks-5 years		156 ± 55
Creatinine clearance (ml/min)			
20	5 days	130 ± 16	138 ± 25
3	9 weeks	130 ± 16	143 ± 9
<10	8 weeks-5 years		156 ± 55
Urea clearance (ml/min)			
20	5 days	57 ± 4	50 ± 4
3	9 weeks	57 ± 4	49 ± 8
<10	8 weeks-5 years		86 ± 8
Albumin clearance (μl/min)			
20	5 days	0.14 ± 0.1	0.16 ± 0.02
3	9 weeks	0.14 ± 0.1	0.15 ± 0.02
<10	8 weeks-5 years		0.15 ± 0.03

* Significantly different ($p < 0.05$) from baseline value.

mal range about 120 to 140 ml/min). Thus, kidney impairment was evident, which was gradually restored after stopping the creatine supplementation.

The only investigations of renal function in healthy individuals who consumed oral creatine supplementation were published quite recently.[107,108,110] We compared the renal clearances of creatinine, urea and albumin in 3 different groups of active individuals who received creatine for 5 days, 9 weeks and up to 5 years with those of control groups. We did not observe statistically significant differences between the control groups and the creatine consumers (table VI). From these experimental protocols we can state that glomerular filtration, tubular reabsorption and glomerular membrane permeability were not affected by oral creatine supplementation using the usual amount (20 g/day for 5 days followed by less than 10 g/day thereafter). Moreover, it is quite easy to determine creatine consumers from the creatine/creatinine ratio in a sample of urine (fig. 1). This ratio is always less than 40 (mg creatine/g creatinine) in nonconsumers and higher than 150 for individuals receiving at least 2g of creatine per day.

Thus, we believe that healthy individuals are not confronted with health risks when consuming reasonable amounts of oral creatine monohydrate. Nevertheless, we urge regular consumers to be tested regularly for excess albumin excretion (>20 μg/min) in urine collected under resting conditions, i.e. after 20 hours of physical inactivity.[111]

However, one case report of interstitial nephritis was published by Koshy et al.[112] in a patient who had taken 20g of creatine daily for 4 weeks. This previously healthy man presented with a 4-day history of nausea, vomiting and bilateral flank pain. The patient was hospitalised with a serum creatinine concentration of 2.3 mg/dl (upper limit of normal range 1.5 mg/dl) and a urine protein excretion of 472 mg/day (upper limit of normal range 150 mg/day). 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 a single case report out of thousands of regular creatine consumers. Nevertheless, it emphasises our recommendation to be tested regularly for urinalysis.

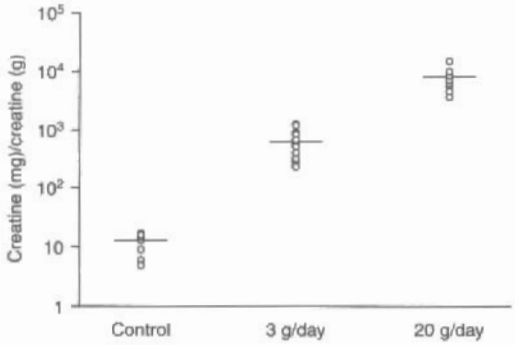

Fig. 1. Urinary excretion of creatine and creatinine, expressed as the ratio of creatine (mg) to creatinine (g) in a urine sample, by control individuals and study participants who ingested creatine monohydrate 3 or 20 g/day.[107,108,110] The horizontal bars represent the geometric means of each population. A clear separation is observed between non-consumers and consumers.

Creatine supplementation has been administered to dialysed patients by Kirschbaum (personal communication) without any adverse effects on blood chemistry.

6. Conclusion and Recommendations

The interest in creatine as an ergogenic aid for athletes has increased over recent years. The purpose of the present study was not to present data and conclusions on the benefit, or the absence of benefit, on sport performance or in various pathological conditions, but to emphasise the potential adverse effects of creatine supplementation in healthy individuals and patients.

It appears that muscle cramping and gastrointestinal distress remain anecdotal. Despite papers and editorials published in the sports media, there is no apparent liver, muscle or kidney dysfunction when healthy individuals consume oral creatine monohydrate at the usual daily amounts (20 g/day for 5 days followed by less than 10 g/day thereafter). Tissues seem to adapt their metabolism by a downregulation of the expression of creatine transporter isoforms, at least in rat skeletal muscle.[113]

Even if there are no health risks induced by oral creatine supplementation, it is best to remain cautious when this substance is administered on a long term basis. Excess creatine ingestion is still a burden to be eliminated, mostly by the kidney. Regular checkups are advisable to detect any potential dysfunction that may appear in some individuals less able to compensate for any homeostatic imbalance.

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