NutritionX

The Nutrition X—CHANGE

06

CREATINE - WHY, WHEN AND HOW TO USE IT

A detailed look at creatine's physiological impacts on the body

Professor Don Maclaren

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Practical Implications

+ Creatine and phosphocreatine are important compounds in skeletal muscle for the provision of energy during short, explosive bouts of exercise.
+ Increasing total muscle creatine is associated with improvements in power, strength, speed, and lean muscle mass.
+ Muscle has an upper limit of total creatine which can be reached by supplementing with creatine. Although creatine is found in meat and fish (not plants), the level of increasing muscle creatine by diet alone is unlikely to be achieved even when consuming large portions of meat/fish.
+ Enhanced muscle creatine concentrations can be attained within 5 days of ingesting 20g/day of creatine or more slowly over a 2-3 week period by ingesting ~5-6g/day.
+ Creatine concentrations in muscle can be maintained by ingesting 2-3g/day once 'loaded'.
+ Once 'loaded' creatine is preferably ingested after exercise bouts.
+ Athletes who are vegetarians or vegans have lower levels of muscle creatine compared with those who eat meat and fish. Consequently, vegetarians and vegans would be advised to consider creatine ingestion to elevate muscle creatine. This may be most beneficial prior to engaging in power, strength, and speed training.
+ Creatine supplementation should be planned for all athletes who wish to maximise training when power, speed, and strength are key components.
+ Caution is required with creatine supplementation for athletes engaged in weight limited sports since ingestion is highly likely to increase body mass.
+ Youth athletes are likely to enhance lean body weight, strength, power and speed with creatine supplementation, although this must be undertaken with parental approval, performing appropriate training, and under the supervision of qualified personnel.
+ Ageing athletes are also likely to benefit from creatine supplementation.
+ Creatine in combination with high carbohydrate intake has been observed to promote muscle glycogen stores and thereby improve prolonged activities. This may be a useful strategy when matches or competitions happen within short periods of time.
+ Emerging evidence suggests that creatine supplementation may help cognitive function and thereby skill and decision-making. This may be particularly important during stressful periods.
+ There is no consistent evidence that one form of creatine is more beneficial than another. In many cases such advertisements are a gimmick!
+ Although it is advisable to use creatine supplementation only when undertaking pertinent training, the long-term use of appropriate amounts of creatine is not a health issue unless athletes have an underlying kidney problem.

Background

Creatine (Cr) is a ubiquitous compound found in muscles of all vertebrates. It plays an important role in ensuring rapid release of energy for intense bouts of exercise. Activities such as weight-lifting, jumping, throwing, punching, and sprinting utilise Cr in producing the required energy. However, the stores of Cr are rather limited and means of enhancing muscle stores may prove beneficial for athletes. This review briefly explains the biochemistry of energy metabolism in order to understand the relevance of Cr for energy production. Evidence is provided to show how muscle stores of Cr can be enhanced before proceeding to explore the attestation for the benefits of Cr in various activities. Figure 1 represents some current thoughts on the likely benefits of Cr supplementation for athletes. The article examines the potential for enhancement of various sporting activities as well as brain function.

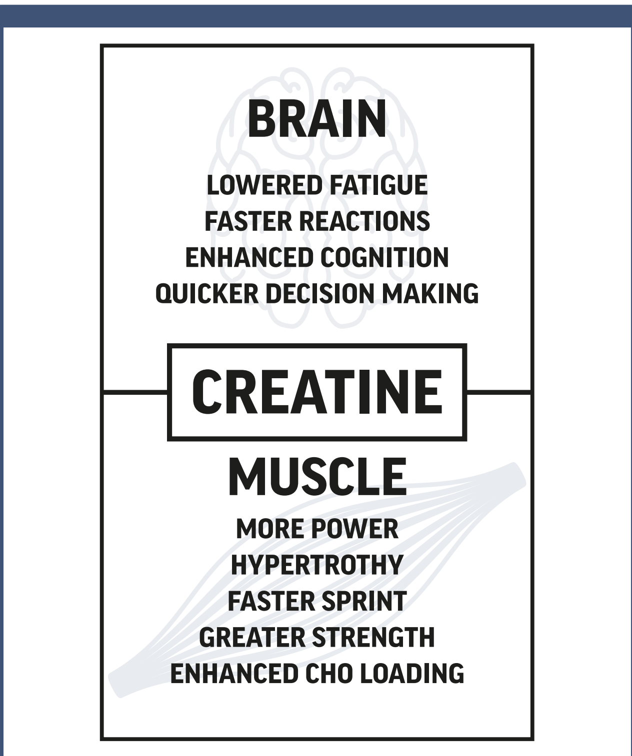

Figure 1. Schema highlighting some potential effects of creatine supplementation on muscle and brain.

The major energy sources for exercise are dependent on the intensity and duration of the activity. Examination of Figure 2 highlights that there are three such sources, i.e. phosphocreatine (PCr), glycolytic and aerobic. These energy-producing processes predominate exercise from 1–10 seconds, 10–60 seconds and beyond 60 seconds respectively.

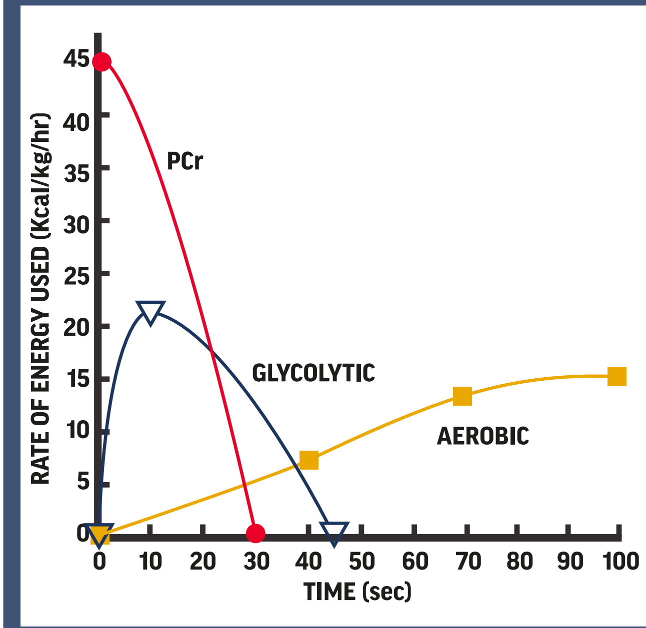

Figure 2. Energy continuum is a schema to highlight 3 major energy systems in skeletal muscle of which phosphocreatine (PCr) is the major contributor for ATP resynthesis in the first 10-20s of intense exercise.

Adenosine tri-phosphate (ATP), which is in effect the energy currency of the cell, is not stored to a great degree in muscle cells. Therefore, once muscle contraction starts, the regeneration of ATP must occur rapidly. There are three primary sources of ATP; these, in order of their utilization, are phosphocreatine (PCr), anaerobic glycolysis and aerobic processes.

Energy from ATP derives from cleaving the terminal phosphate of the ATP molecule. The resulting molecule is adenosine diphosphate (ADP). Phosphocreatine converts ADP back to ATP by donating its phosphate in the presence of the enzyme creatine kinase (CK), and in turn the PCr forms Cr.

$$\mathrm{ADP} + \mathrm{PCr} \underset{\mathrm{CK}}{\longleftrightarrow} \mathrm{ATP} + \mathrm{Cr}$$

The reaction of PCr with ADP to form ATP is very rapid, but is short-lived since the cell does not store high amounts of PCr (the muscle concentration of PCr is about 80 mM/kg dry muscle or 120 g in total). However, during short, high-intensity contractions, PCr serves as the major source of energy. This form of energy generation is sometimes referred to as anaerobic alactic, because it neither produces lactic acid nor requires oxygen. The PCr reaction is of paramount importance in sports requiring bursts of speed or power, such as sprints of 1–10 seconds, lifting weights, engaging in a high/long jump, or a throw in an athletics field event.

Figure 3 provides a schematic to show the synthesis of ATP from ADP using PCr at the muscle crossbridge, and also the regeneration of PCr from Cr by ATP at the mitochondria. This is known as the 'PCr shuttle'. Thus, Cr is produced from PCr during intense bouts of exercise, while Cr is re-phosphorylated to PCr by ATP produced in the mitochondria during the aerobic recovery phase. Oxygen is needed for recovery of PCr, as can be seen in Figure 4, which clearly demonstrates that recovery of exercise-depleted PCr only happens when the blood supply to the exercising muscle is not occluded, i.e. there is an intact blood supply taking oxygen to the cells. If the blood supply is occluded (e.g. via a tourniquet), then PCr resynthesis fails. As a consequence, there is the need for a low level (so called active) recovery in between bouts of intense exercise.

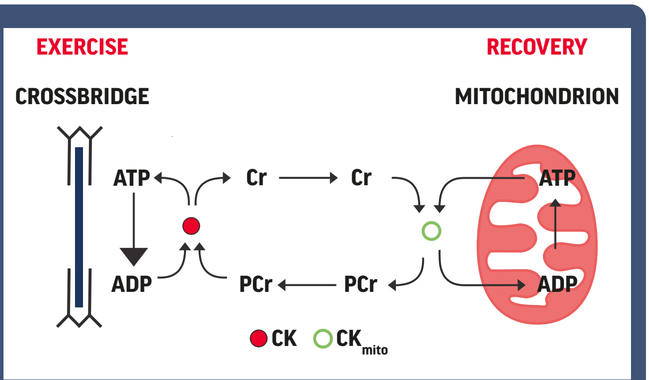

Figure 3. PCr shuttle illustrates the conversion of Cr to PCr from the mitochondria after the formation of Cr from PCr at the crossbridge when a muscle contracts.

The enzyme CK, which regulates PCr activity, exists in a number of forms known as isoforms. Note that not only is there a CK which favours the formation of ATP from PCr, but there is also another form, CKmito, which is present at the mitochondria and favours the synthesis of PCr from Cr using ATP. In effect, the same enzyme (CK) but in different isoforms which results in either the breakdown or synthesis of PCr.

You should also note from Figure 4 that there is a rapid loss of PCr during intense exercise and that it is rapidly recovered (PCr stores may even be depleted if the exercise is sufficiently intense or prolonged). Nearly 75% of PCr is resynthesized within the first minute of recovery and the rest over the next 3–5 minutes. The graph is biphasic, i.e. rapid restoration at first, then a second, slower phase.

The use of PCr is maximal in the first fifteen seconds of high intensity exercise and thereafter decreases as first glycolysis and then aerobic sources predominate. It has been demonstrated that during a 6-second sprint on a cycle ergometer, PCr contributes approximately 50% of the total ATP production (Boobis, 1987).

Fatigue as a consequence of high intensity exercise

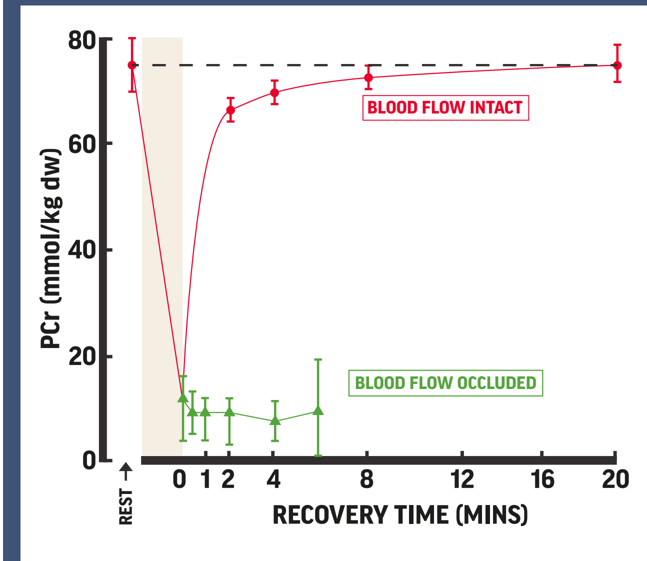

Figure 4. Resynthesis of PCr after exercise with and without an occluded blood supply highlights the need for oxygen in restoration of PCr, and so demonstrates the importance of the aerobic system in recovery (adapted from Hultman et al., 1990).

is a complex phenomenon. In essence, fatigue is based on the inability to sustain the necessary power output, which means a reduction in ATP cycling caused by some factors. These include the likelihood of depletion of PCr stores in type IIx (fast twitch) fibres, increases in Pi, and/or increases in H + concentration in the muscle causing acidosis. The increase in H+ is a subject of debate and will not be explored in this article (please read more in volume 2 of The Nutrition X-Change on beta-alanine). If we exclude factors associated with acidosis and H+ increases in muscle, a potential ergogenic aid likely to have an impact on muscle fatigue during intense exercise would be in elevating PCr through Cr supplementation.

Creatine

Creatine (Cr) has been known as a constituent of food for over 150 years. However, it was not until

the early 1990s that significant levels of research were undertaken examining the effects of creatine supplementation on sports performance. Creatine, or methyl guanidine-acetic acid, is a naturally occurring nitrogenous molecule found mainly in the skeletal muscles of vertebrates. It is also found in smaller amounts in liver, kidney, and brain. Although found mainly in skeletal muscle, Cr is metabolised in the liver, kidney and pancreas, and then transported to muscle and brain (Figure 5). This is due to the fact that most tissues lack several of the enzymes involved in creatine synthesis.
Three amino acids are involved in the synthesis of creatine, these being arginine, glycine, and methionine. De novo synthesised Cr is transported from the liver to skeletal muscle where it is taken up by active transport using a Na+-dependent transporter. Once inside the muscle cell the Cr is 'trapped' by being converted to PCr, which is unable

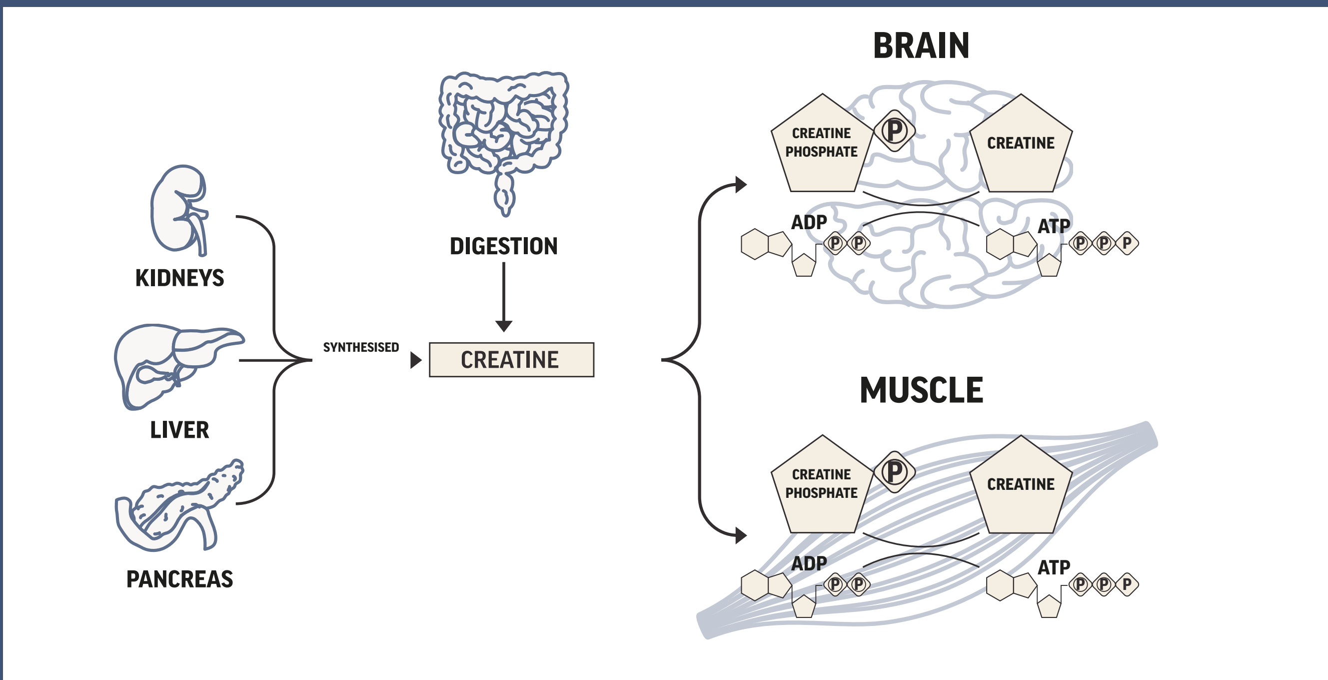

Figure 5. Creatine is produced in the liver, kidney, and pancreas from which it is transported to muscle and brain. Once inside the muscle and brain the Cr is phosphorylated to PCr and ready for use as an energy source.

to pass through the membrane. Approximately 70% of the creatine in muscle is in the phosphorylated form PCr, the other 30% being free Cr.

Creatine is constantly degraded to creatinine, which is its sole end product, via a non-enzymatic irreversible reaction. The creatinine diffuses through the muscle membrane and is taken to the kidney where it is excreted in a passive process before being voided in urine. The daily urine creatinine excretion is relatively constant, although it varies between individuals due to differences in muscle mass. The daily turnover of Cr to creatinine in humans is about 2 g/day for a 70 kg person, and is replaced by endogenous synthesis and exogenous sources in the diet. Synthesis is regulated by the exogenous intake through a feedback mechanism.

About 95% of the Cr pool can be found in skeletal muscle, although significant amounts can also be found in heart, spermatozoa, brain, seminal vesicles, macrophages, and photoreceptor cells of the retina. Low levels of Cr are present in kidney, liver, spleen, and lungs. The stores of Cr exist in both the free and phosphorylated (PCr) forms. Total muscle Cr concentration is approximately 120 mM/kg dm in muscle. Note that total Cr concentration includes the phosphorylated form. Factors such as age, sex, and diet influence muscle Cr concentration. Resting PCr levels have been shown to be lower in older (60 year) compared with younger (30 year) subjects (Smith et al., 1998), although there is no significant difference in the total Cr concentration. In this instance it is possible that the degree of inactivity in the older subjects may have led to the attenuated PCr levels. Females have been reported to have an elevated Cr concentration compared with males (Forsberg et al., 1991). Diet can significantly influence muscle Cr concentration.

However, it should be noted that since the exogenous source of Cr is via consuming foods containing meat and fish, vegetarians may have lower concentrations since their only source is de novo synthesis. Studies have shown that vegetarians have marginally lower muscle Cr concentrations than those who eat meat and fish (Delanghe et al., 1989; Harris et al., 1992).

Another influence on muscle Cr is that of training. The results from training studies have been equivocal, although Bernus et al. (1993) established that sprint trained athletes had elevated concentrations of PCr when compared with endurance athletes. In this instance the differences could be due to the muscle fibre composition of the athletes, although the effect of training cannot be overlooked. Results from longitudinal training studies which have employed sprinting or resistance modes have failed to show elevated levels of PCr or Cr (Nevill et al., 1989; Sharp et al., 1986).

Muscle creatine 'loading'

Muscle Cr is restored at a rate of approximately 2 g/day by a combination of dietary Cr ingestion from sources such as meat and fish, and from endogenous synthesis. Muscle Cr content has been found to increase significantly following creatine ingestion (Harris et al., 1992). In this study, ingestion of 5 g of Cr 4-6 times a day for five days resulted in an increase in total Cr from 127 to 149 mmol/kg. These increases were individual, with some subjects increasing their Cr significantly and others less so. The term 'responders' and 'non-responders' applies in this instance, and a relationship between the initial resting level and the level of increase was established. Two vegetarians in the study possessed the lowest initial resting concentrations and responded with significant increases. Furthermore, Harris et al (1992) were also able to demonstrate that whereas on the first 2 days the Cr storage was approximately 30% of that ingested, the amount stored in the following 2 days was diminished to around 15% of the Cr ingested (see Figure 6). Studies have shown that muscle Cr concentrations can be significantly enhanced using lower daily doses for a prolonged time period. Hultman et al. (1996) reported that Cr ingestion of 3 g/day over a 4-week period produced muscle Cr concentrations similar to those found when 20 g/day were ingested over a 5-day period. So, creatine 'loading' can take place over a concentrated or more prolonged period of time dependent on dosage per day (Figure 7).

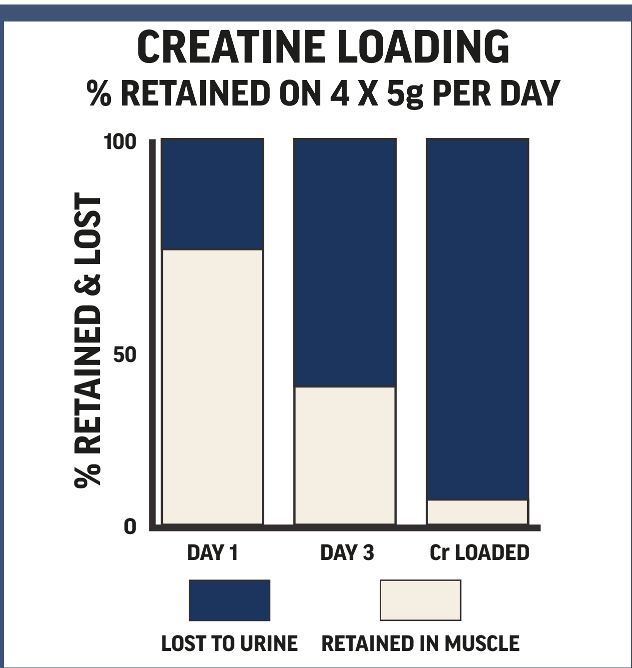

Figure 6. Creatine is retained in muscle significantly in the first few days of 'loading' and thereafter more is excreted rather than retained.

There is considerable variation between subjects to the extent muscle Cr concentrations are elevated following supplementation, although it appears that there is an upper limit of 160 mmol/kg dry muscle. Early evidence showed that ingesting Cr with carbohydrate (CHO) results in the greater possibility of achieving maximal levels of total muscle Cr. It seems likely that the increase in muscle Cr stores when taken with CHO is as a result of insulin action probably by stimulating the Na+-dependent muscle Cr transporter activity. A specific, saturable, Na+-dependent transporter responsible for Cr uptake across the plasma membrane has been described for skeletal muscle, heart, brain, kidney, intestine, and red blood cells, but not for liver. Therefore, it is suggested that creatine should be ingested in combination with a carbohydrate meal or drink (Green et al., 1996).

Following the Cr loading phase of 20 g/day for 5 days, recommended maintenance doses are considerably lower. Most studies have used doses ranging from 2 to 5 g/day during the maintenance phase in order to ensure the intake matches or is greater than renal excretion. When an athlete stops ingesting Cr, the muscle Cr levels diminish to normal levels after 4 weeks (Greenhaff, 1997; Hultman et al., 1996).

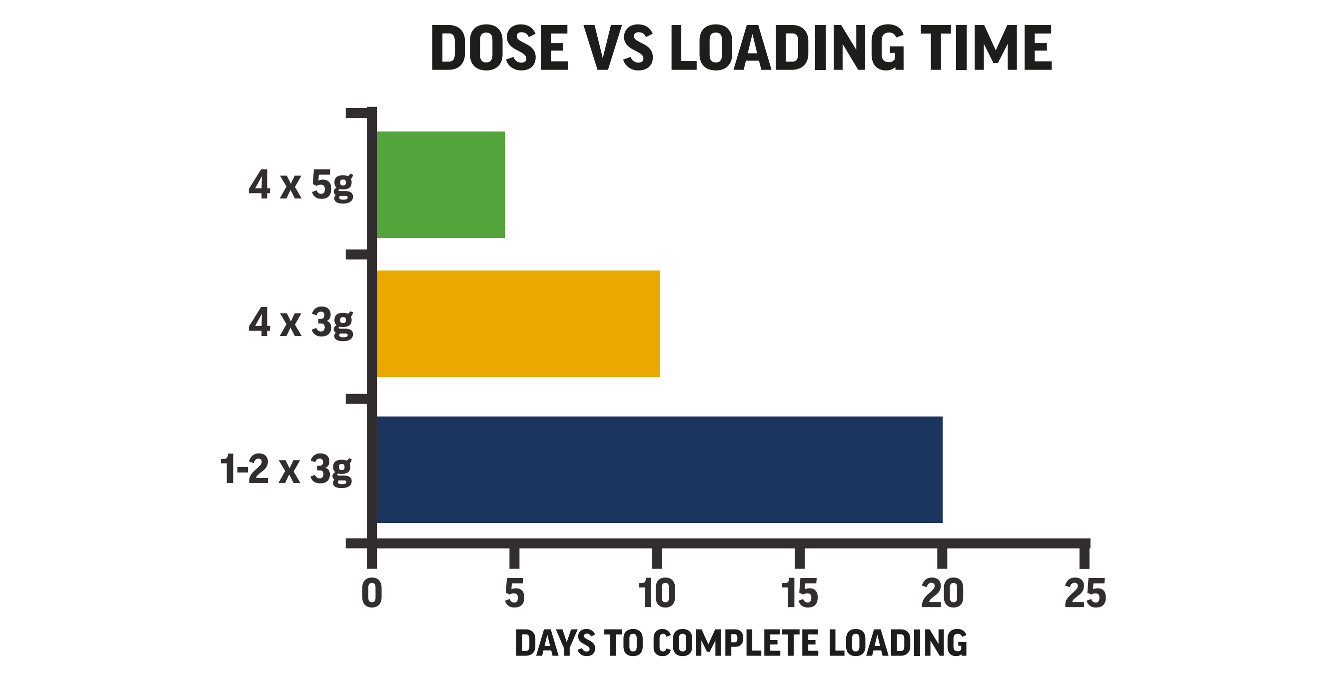

Figure 7. Total muscle creatine can be achieved by taking 20g/day over 5-days or lower doses over a longer period. The end-result is a similar total muscle Cr content.

Creatine and performance

The theoretical benefits of Cr supplementation are related to the role of Cr and PCr in the energetics of muscle contraction, and also to the potential for buffering increases in [H+] as a consequence of raised intramuscular lactic acid concentrations. Specifically, mechanisms purported to provide an ergogenic effect of creatine include the fact that supplementation results in elevated PCr levels in muscle and hence a greater immediate source of generation of ATP, that increased levels of Cr would facilitate an enhanced rate of PCr resynthesis in recovery bouts, and that there is enhanced buffering of H+.

Intramuscular stores of ATP and PCr are limited, and it has been estimated that these phosphagen stores could supply sufficient energy for high-intensity exercise for not more than 10 seconds (Balsom et al., 1994). Furthermore, Sahlin (1998) has suggested that the maximum rate of PCr hydrolysis decreases as PCr content of muscle decreases, and that complete depletion is not necessary to cause a reduction in power production. In fact, a number of researchers have concluded that PCr availability is a limiting factor during high-intensity exercise (Greenhaff, 1997; Balsom et al., 1995; Ruggeri et al., 2000).

Creatine supplementation, by increasing both Cr and PCr, particularly in the fast glycolytic fibres, should prolong either single bouts of high-intensity exercise and in particular repeated bouts of high-intensity exercise. Probably the first two studies which reported on Cr supplementation and intense exercise were those of Greenhaff et al. (1993) and Balsom et al. (1993). Greenhaff and colleagues (1993) employed 5 bouts of 30 maximal isokinetic knee extensions with 1 minute recovery between the bouts. When subjects were loaded with 20 g/day of Cr for 5 days, peak muscle torque was significantly enhanced in the final 10 contractions during the first bout, and during the whole of the next 4 bouts.

Balsom et al. (1993) used ten 6 second bouts of high-intensity cycling with 30 seconds recovery between the tests. Subjects were expected to maintain a pedal rate of 140 rpm with a resistance set so that they could complete 6 seconds. The creatine-loaded group were able to maintain 140 rpm in the last 2 seconds of each of the bouts, whereas those on placebo failed to do so after the 4th bout of cycling.

Since these early reports, in excess of 500 studies have been published in peer reviewed articles. The majority of these studies highlight the effectiveness of Cr supplementation for enhancing sports performance (Bemben & Lamont, 2005; Hespel & Deravez, 2007; Kreider et al., 2017; Mielgo-Ayuso et al 2019) and also of being of potential use for ageing athletes (Tarnopolsky, 2008). These studies have examined the effects on high-intensity exercise (both single bouts and repeated bouts), strength and power, field-based activities, and endurance (Deldicque & Francaux, 2008). Other studies have purely examined the effects of supplementation on lean body mass and body composition, although many of the other studies have also reported data on body mass changes.

CREATINE AND SINGLE BOUTS OF HIGH INTENSITY EXERCISE

Since Cr supplementation leads to increases in muscle Cr and PCr, it would be expected that single bouts of high intensity exercise would enhance performance. However, this is not always the case. Some studies have shown significant improvements in sprint running (Goldberg & Bechtel, 1997; Kendall et al., 2009; Law et al., 2009; Noonan et al., 1998), or vertical jump performance (Stout et al., 1999), whereas many studies using single bouts of running, cycling, swimming, and jumping have failed to show significant improvements when Cr loaded. It appears that the possibility of elevated Cr stores in muscle being available to maintain a short, sharp burst of activity when not fatigued does not always happen. Interestingly, in a study in which a single bout of 10 seconds of sprint cycling was assessed following 5 bouts of 6 s sprinting with a 30 s recovery between bouts, an increase in power was observed (Balsom et al., 1995). So, when there is an element of fatigue due to previous activity, creatine may help to improve single bouts of intense exercise. This is also the case with respect to soccer performance whereby there is no evidence of creatine having an influence on overall match performance but significant faster sprints can be observed at points during the match.

CREATINE AND REPEATED BOUTS OF HIGH INTENSITY EXERCISE

Since enhanced stores of Cr and PCr result from creatine loading, there is the possibility that during recovery phases of repeated bouts of exercise, the elevated Cr will be more rapidly phosphorylated to PCr. Enhanced performance may then result in subsequent bouts of exercise. Positive ergogenic effects of Cr loading have been exhibited for repeated bouts of high intensity cycling (Balsom et al., 1993; Earnest et al., 1995), running (Aaserud et al., 1998), swimming (Peyrebrune et al., 1998), and vertical jumping (Bosco et al., 1997). In most cases, the significant effects are noted in the later bouts of exercise and not usually in the first bout. Furthermore, the effects are normally associated with mean power or total work done rather than peak power values. All in all, these findings do support the notion of greater re-phosphorylation in the recovery period when Cr stores have been enhanced.

It should be noted however, that not all studies have reported significant effects. Some studies on repeated sprint cycling have shown no significant effect of Cr ingestion (Barnett et al., 1996; Cooke et al., 1995). Similar non-responses were obtained for investigations using repeated running (Smart et al., 1998), and swimming (Leenders et al., 1999).

It is difficult to fathom out the reasons why the majority of studies highlight positive ergogenic effects whereas a significant, though smaller, number find no such differences. Examination of the dose of Cr ingested and whether carbohydrates were ingested, together with the types of subjects used (i.e level of training), the sex of the subjects, the dietary habits of the subjects, the number of subjects employed, and variations in the mode of testing are all possible confounding variables. On balance, Cr supplementation results in an approximate 4-10% improvement in repeated high intensity activities. Even some of the studies which reported no significant findings, reported 2-4% improvements in performance, but due to the low power of the experimental design produced non-significant results.

CREATINE AND STRENGTH

Phosphocreatine and ATP are likely to be the major energy sources during strength-based activities which are isometric, isotonic, or isokinetic. In the cases of isotonic or isokinetic exercise, the activity is repeated in either fast or slow modes, whereas isometric activity involves either an all-out fast action or a hold of the tension for a period of time. The majority of studies in which some form of strength has been assessed, have shown positive ergogenic effects of Cr supplementation. Such studies include the use of isometric (Maganaris & Maughan, 1998), isotonic (Earnest et al., 1995; Noonan et al., 1998), or isokinetic (Greenhaff et al., 1993; Vandenberghe et al., 1996) modes of testing. Improvements of between 6 and 28% in strength were reported in the above studies. Recent studies in the elderly have shown the potential for significant improvements in strength and lean body mass with creatine ingestion (Tarnopolsky, 2008). It has been proposed that Cr supplementation augments the increase in satellite cells and myonuclei in skeletal muscle induced by strength training (Olsen et al., 2006). However, as with the studies on repeated bouts of high intensity exercise, there are a number of studies which reported no significant benefits of creatine on isometric strength (Rawson et al., 1998), isotonic strength (Stout et al., 1999), and isokinetic strength (Kreider et al., 1996). The reasons for discrepancies in these findings maybe those expressed above, but in addition could include the level of resistance or weight training experienced by the subjects. The latter seems unlikely since studies showing positive effects have included experienced and novice subjects, as have those showing no significant effect. Again, on balance the evidence for a positive effect is greater than no effect.

CREATINE AND ENDURANCE PERFORMANCE

In spite of the fact that Cr and PCr are involved in high-intensity and anaerobic energy requiring activities, there has been some speculation that Cr supplementation may help more prolonged, aerobic events due to an enhanced interval training effect which may lead to an increase in TCA cycle enzyme activity i.e. citrate synthase (Greenhaff et al., 1997; Viru et al., 1994, Volek et al., 1999). Of course, a potential 'down side' for running events would be the potential increase in body mass. Smith et al. (1998) used 15 subjects in a study which employed cycling to exhaustion at 3.0, 3.3, and 3.7 watts/kg. Following Cr supplementation of 20 g/day for 5 days, the subjects only improved time to exhaustion at 3.7 watts/kg. No significant effect was noted for the other two exercise intensities. Since the time to exhaustion for the trial using the highest work load improved from 236 s to 253 s, the event may be considered aerobic. The greater the aerobic contribution the less likely creatine is to have an effect.

In spite of the above findings, Bosco et al (1995) found that their subjects improved their Cooper 12-minute run/walk test following Cr supplementation of 5 g/day for 42 days. Furthermore, Viru et al. (1994) found that middle distance runners improved their total time for four 1,000 m interval runs.

In many studies which have examined longer duration activities, no significant effects of creatine have been observed (Godly & Yates., 1997; Myburgh et al., 1996; Stroud et al., 1994). This may be due to the likely increase in body mass normally attained when muscle Cr is loaded and the adjunct of additional stored water.

It would appear that Cr supplementation may have positive effects on intense activities for up to 4 or even 12 minutes where there is a clear involvement in aerobic energy processes. The case for beneficial effects on longer duration events is not demonstrably proven. Clearly there is a need to examine the effects of interval training with and without Cr supplementation to note if there are any ergogenic effects with the combination of more intense training possibly brought about by Cr loading.

CREATINE AND BODY COMPOSITION

One of the proposed ergogenic effects of Cr supplementation is the increase in lean body mass. This may result from the fact that creatine is osmotically active and hence increases the muscle water stores thereby leading to enhanced protein synthesis. Of course, the increase in muscle mass could also result from an increase in training intensity brought about by enhanced muscle stores of PCr and Cr. Williams et al. (1999) reported that out of 58 studies which assessed body mass changes with Cr supplementation, 43 reported significant increases in body mass whereas 15 reported no significant changes. Those studies which reported the increase in body mass showed that a 5 - 6 day loading regimen resulted in an increase of around 1.0 kg (range from 0.6 kg to 2.8 kg). The more long-term studies reported increases in body mass of up to 5 kg in 12 weeks. In the first instance, the changes may be attributed to fluid retention, although subsequent increases were due to enhanced lean body mass.

There is clear evidence in studies which have used resistance training and Cr supplementation, that significant increases in muscle mass have resulted. This is obviously desirable in sports where an increase in muscle mass is important, but not of benefit in sports such as distance running.

Vegetarians and Vegan athletes

As previously mentioned, one of the confounding variables in the likely 'success' of using creatine is related to the level of Cr in the muscle. Invariably, vegetarian and vegan athletes have lower levels of Cr due to the fact that Cr is only present in animal tissue and not plants. Therefore, people following a vegetarian or vegan diet manufacture their muscle Cr via liver metabolism (see earlier) and this is limited. Consequently, when Cr is ingested there is a greater likelihood of a significantly higher increase in total muscle Cr than a meat-eating individual. This can be seen in Figure 8, which is a schema showing proposed variations in total muscle creatine after creatine 'loading' in types of individuals based on their normal dietary intakes.

Creatine and youth athletes

The use of Cr is not limited to adults since there is ample evidence that adolescents in various sports have used creatine (Jagim et al., 2018). The result from a series of published surveys on USA adolescents reported that between 5–20% of middle school and high school aged individuals took Cr at some point. Interestingly, Cr use was consistent at ~4% in grades 6–10 while substantially increased to 10-40% in grades 11 and 12. Examination of prevalence among adolescent athletes reveals similar trends in so far as Cr is often listed as one of the more commonly used dietary supplements among this population (Jagim et al., 2018). Males appear to be more likely than females to report using Cr and the most commonly reported reasons for supplementation often include a desire to increase lean body mass and for increased energy production. Consequently, strength, power, and sports which require significant energy from anaerobic sources such as American football, wrestling, and ice hockey appear to have the highest rates of use. Anecdotally, my own experience when giving lectures to Academy players, parents, and coaches in soccer or rugby reflect the significant interest in the possible use of Cr.

Despite the overwhelming supportive body of literature regarding the efficacy of creatine supplementation in adult athletes, limited data are available for adolescent athletes. This lack of available literature is probably due to ethical restrictions and safety concerns. Having said that, the physiological basis for creatine use in adolescents is that "in anaerobic athletes, there exists a metabolic rationale as to how and why creatine may provide an ergogenic benefit" (Unnithan et al., 2001). Additionally, the International Society of Sports Nutrition in their position statement on creatine use (Kreider et al., 2017) recommended that younger athletes should consider a creatine supplement if certain conditions were met. These included approval from parents, selection of quality supplements, abiding by recommended dosing instructions, and ensuring that diet was optimized

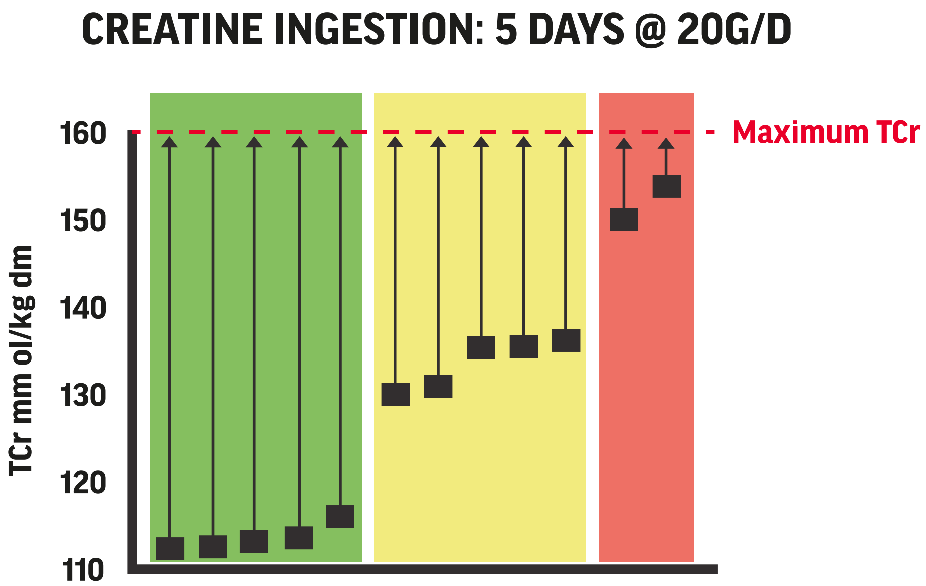

Figure 8. Total muscle creatine in meat/fish eaters (red), more mixed eaters (yellow), and vegetarians (green).

prior to supplementation.

The earliest study reporting the efficacy of creatine in young athletes was performed on swimmers (Grindstaff et al., 1997). Eighteen male and female swimmers aged ~15yo were randomly assigned to one of two groups to ingest either 21 g/day of creatine or placebo over a period of 9 days. Significant improvements in repeat sprint performance were observed following creatine supplementation. Similar findings were seen for 16-yo competitive swimmers after 5-days of supplementation in swim performance and dynamic strength (Juhasz et al., 2009). However, a similar study on ~16yo swimmers in which the creatine was taken over 28-days failed to show a significant benefit.

In land-based sports, 7 days of creatine supplementation were found to improve soccer specific drills in ~16-yo male soccer players (Ostojic et al., 2004). Likewise, significant improvements in repeat sprint performance and dribbling abilities were observed in 7-day creatine supplemented 17-yo soccer players (Mohebbi et al., 2007), and more recently17-yo soccer players had significant improvements in power output following a low-dose creatine supplementation regimen (0.03 g/kg/day) for 7 days (Yanez-Silva et al., 2017).

The evidence for effective creatine supplementation in adolescents is similar to efficacy for adults in appropriate sports. It is unlikely to prove beneficial for those who have not gone through puberty both from an ethical perspective but also from the point of view that pre-pubertal children do not appear to have well developed anaerobic energy producing systems. Post-pubertal adolescents could benefit as long as good eating habits are primarily undertaken, that parental guidance is provided, and that supervision from a qualified nutritionist is assured.

When should creatine be ingested?

The timing of creatine ingestion may be an important factor contributing to the physiological benefits observed with creatine supplementation (Candow et al., 2015). For example, ingestion of creatine (0.1 g/kg or 8 g) immediately before and immediately after resistance training sessions for 12 weeks was shown to increased muscle mass and strength in healthy older adults (Candow et al., 2014). Likewise, a marginally earlier study in young males observed greater increases in muscle mass and strength with post-exercise Cr ingestion than if ingested before exercise (Antonio and Ciccone, 2013). Furthermore, consumption of a supplement containing Cr before and after resistance training sessions for 10 weeks resulted in greater increases in lean tissue mass and cross-sectional area of type II fibres than consumption of the Cr supplement in the morning and evening on exercise training days (Cribb and Hayes, 2006). Finally, most recently Candow et al. (2015) using a

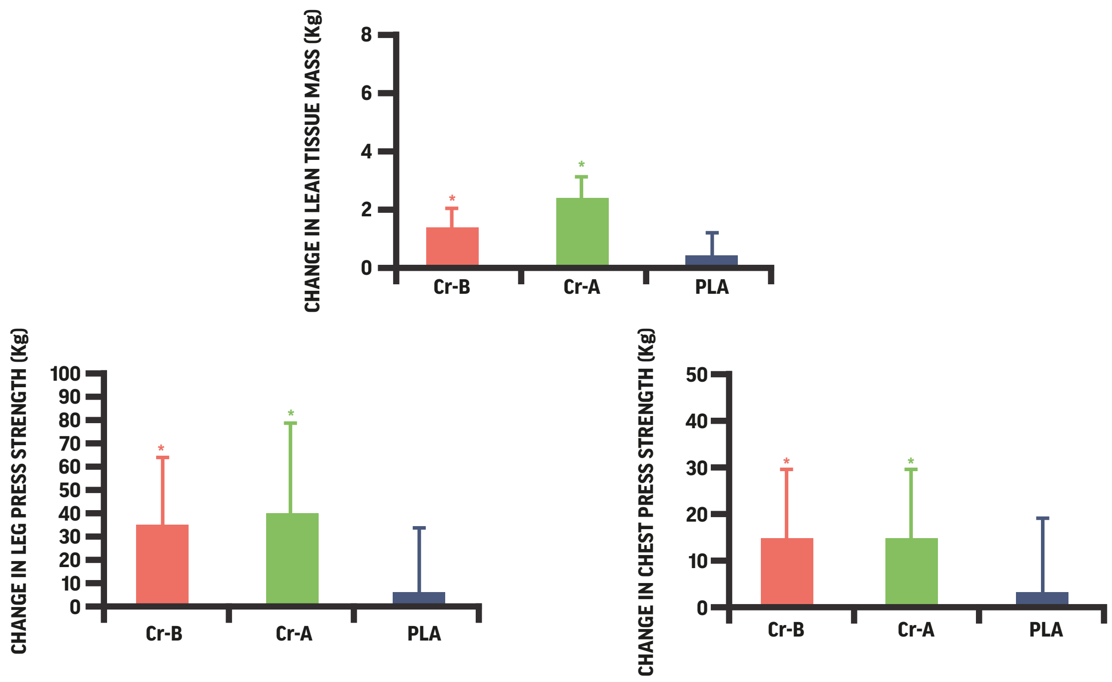

Figure 9. Changes in lean tissue, chest press and leg press after Cr before (CR-B), Cr after (CR-A), and Placebo (PL). (Adapted from Candow et al., 2015).

3-arm protocol of training and supplementation (i.e. Cr before, Cr after, and placebo) demonstrated that post-training supplementation of Cr over a 32-week period resulted in greater muscle mass than the other 2 conditions, and that both Cr treatments enhanced leg and bench press strength greater than placebo. Figure 9 highlights the key findings.

Creatine and carbohydrate

Creatine ingestion has been employed with carbohydrate in order to help store muscle glycogen. The first investigation to report that creatine supplementation augments post-exercise muscle glycogen storage used a conventional 'CHO-loading' regimen and observed that this response was restricted to the exercised limb (Robinson et al. 1999). This study also confirmed this Cr-mediated augmentation of post-exercise muscle glycogen storage was sufficient to produce a significant improvement in subsequent endurance performance. These findings have since been supported by other similar investigations (Nelson et al., 2001; Roberts et al., 2016; Sewell et al., 2008; Van Loon et al. 2004). It may be pertinent to consider a combination of Cr and CHO in order to augment glycogen storage in muscles during periods of intense training or when many competitive matches are to be played such as over the Christmas period in the UK for soccer. Anecdotally, I have undertaken such a strategy (successfully – at least with regard to distances covered during soccer matches) over Christmas periods with Premiership football clubs.

More recently, a study exploring the efficacy of Cr supplementation followed by CHO loading for 2-days prior to cycle time trial (TT) performance observed no difference in pre-TT muscle glycogen between Cr and placebo yet a faster final 4-km bout with Cr (Tomcik et al., 2018). The implication from these data are that whereas muscle glycogen loading enhanced TT performance compared with baseline, the enhanced provision of total muscle Cr was the key driving factor for improvements in the latter stages of the TT and not muscle glycogen per se. So, it would seem that elevated muscle Cr stores can contribute significantly to high intensity bouts in a more prolonged setting, and this was in spite of an elevation in body mass. Although the increase in body mass may not seem too pertinent in cycling, it would probably be a greater disadvantage in running activities. Why the muscle glycogen stores were similar between Cr loaded muscles and 'normal' level muscles is unclear.

Creatine and the brain

Although most of the total body creatine is found in skeletal muscle, the brain is also a metabolically active tissue, accounting for up to 20% of the body's energy consumption. Creatine kinase is also expressed in a brain-specific isoform (BB-CK), suggesting that Cr may also be relevant for energy provision to the central nervous system (CNS). In fact, creatine-deficient syndromes involving brain Cr depletion are characterized by major mental and developmental disorders such as mental retardation, learning delays, autism, and seizures, which may be partially reversed by Cr supplementation. Cognitive processing may also be affected by creatine metabolism, as it may facilitate ATP homeostasis during periods of rapid or altered brain ATP turnover, such as during complex cognitive tasks, hypoxia, sleep deprivation, and some neurological conditions. It is beyond the scope of this article to explore the potential role of Cr on brain function and so the reader would be advised to read more substantial reviews in this field (Rae et al., 2015; Avgerinos et al., 2018)

An additional point worthy of note is the potential for Cr supplementation to somewhat attenuate concussion and brain trauma injuries. Some studies have observed positive findings with regard to Cr supplementation for recovery from traumatic brain injury including reduced duration of post traumatic amnesia (PTA), duration of intubation, and intensive care unit stay. Significant improvement were also noted for headaches, dizziness and fatigue in all patients, with no side effects were seen due to Cr administration (Sakellaris et al., 2008). It appears however, that no studies have yet been undertaken examining Cr supplementation prior to sports in which head injuries are more likely to occur such as boxing, rugby, soccer and so on. For a more in-depth perspective on this topic it is pertinent to consult Dean et al., (2017).

Health related aspects

Since excess Cr is excreted by the kidneys, consideration from a health perspective should be given to Cr and kidney function.

A few examples of health-related problems linked to Cr and kidney function have arisen (mainly) in the press. The first reported problems were published in late 1997 and early 1998. In the first instance, the death of 3 US collegiate wrestlers from renal failure were reported to be linked to Cr supplementation. In fact, only one of the wrestlers had used creatine. The probable cause of renal failure was due to the extreme weight loss measures undertaken by these athletes in order to make weight for competition. Nonetheless, these tragic deaths brought to light the potential for renal problems if athletes engage in loading with creatine over prolonged time periods without adequate hydration. Juhn et al. (1999) reported that many male collegiate athletes ingested greater than 10 g/day of Cr. This is ill-advised, and if taken in conjunction with diuretics or other dehydration strategies, could conceivably place a strain on the renal system. Having said that, evidence of athletes consuming 10 g/day (or more) over 9 weeks failed to show impairment of renal function as measured by creatinine clearance, serum concentration of creatinine, and urine analysis (Poortmans & Francaux, 1999).

Another case, which was reported in the Lancet in 1998 (Pritchard & Kalra, 1998), concerned the effects of Cr loading and maintenance over a 7-week period in an amateur football player who suffered from focal segmental glomerulosclerosis. Creatine supplementation resulted in a fall in creatinine clearance, and so gave concern to the physicians. It appears that in this instance, when an athlete has a recognised kidney dysfunction, they should be wary of supplementing with creatine.

In spite of the anecdotal report on the 3 wrestlers, and the 2 case studies reporting renal problems, Poortmans et al. (1997) and Poortmans & Francaux (1998) have shown no significant effects on kidney function when creatine is taken over a short or long period. Indeed, Schilling et al. (2001) published a retrospective study on 26 collegiate athletes who supplemented their diets with creatine. They concluded that all the subjects' kidney function tests fell within the normal range. It appears that even after 25 or more years of research on Cr supplementation, there is no actual evidence relating to negative health outcomes.

Some clinical studies have added to the debate on safety of Cr supplementation over prolonged periods of time.

In one study, the continuous use of lower doses (1.5 g/day) of creatine over a 5-year period for patients suffering from gyrate atrophy of the choroid and retina have shown no adverse effects on kidney or liver (Vannas-Sulonen et al., 1985). Furthermore, studies on children who are born with an inability to synthesise creatine and so have diminished muscle and brain creatine stores, suffer impaired motor and mental function. Treatment with oral Cr supplementation of between 4-8 g/day over 2 years resulted in normalised muscle and brain stores, which in turn led to normal physical and mental development. In these cases no reports of renal or liver damage was found (Stockler et al., 1994; 1996).

Anecdotal reports of Cr supplementation causing muscle cramps, gastrointestinal (GI) problems, and muscle injuries have been stated in various newspaper and leisure articles without strong scientific backup. Kreider et al. (1998) found, in a retrospective analysis of 5 of their published studies, that reports of GI distress were isolated and fewer than for subjects taking the placebo supplement. This finding is supported by the retrospective study of Schilling et al. (1999).

The results from several studies have refuted the anecdotal reports of Cr supplementation leading to dehydration and thereby causing muscle cramps (Hultman et al., 1996; Hunt et al., 1999; Kreider et al., 1996; 1998a; Rasmussen et al., 1999). Indeed, some of these authors report the potential beneficial influences on body water retention rather than enhanced dehydration and muscle cramps.

The majority of studies in which Cr supplementation has been employed have not reported significant problems either in the form of renal function, or in matters relating to muscle cramps or GI disturbance. When an athlete with normal kidney function uses creatine in a sensible manner there does not appear to be a problem. Ensuring that a dose of 3-10 g/day for the maintenance phase with sufficient volume of fluid is a minimum safety requirement. Seeking medical advice on renal function is a useful adjunct.

Therapeutic role of Creatine

In addition to the ergogenic value of creatine, there has been an emerging interest in the clinical application of creatine. Creatine has been cited as a potential adjuvant therapy for the treatment of a variety of diseases such as myopathies, dystrophies, inflammatory diseases, neurodegenerative disorders, metabolic disturbances, and joint syndromes (Gualano et al., 2010). With advancing understanding, it is clear that the function of creatine goes beyond that of a primary role in metabolism and energetics. In fact, recent evidence indicates that creatine supplementation results in a multitude of non-energy-related beneficial effects on a wide range of cellular targets. Among these promising effects includes the antioxidant potential of creatine, scavenging and neutralizing the reactive oxygen species (ROS) that underly many pathologies (Clarke et al., 2020).

Despite the scientific literature supporting the use of creatine for performance enhancement and for the potential treatment of pathologies, the possible application of creatine supplementation for the improvement of vascular health is also being explored. With this being said, some studies have elucidated that creatine supplementation may be able to attenuate factors such as homocysteine, inflammation, and damaging reactive oxygen species (ROS); all of which, if left uncontrolled or circulating in augmented amounts, have been associated with heightened cardiovascular disease (CVD) risk and compromised vascular health (Clarke et al., 2020).

Conclusion

The use of Cr as a dietary supplement is prevalent across amateur and professional athletes alike. Supplementation with Cr has been advocated to improve both short-term and intermittent high intensity exercise, augment strength and power, increase lean body mass, elevate muscle glycogen stores, and even enhance brain function (particularly when fatigued). Currently, no scientific evidence exists to showing unfavourable effects, even when supplementation is prolonged, providing correct protocols are followed and the participant is otherwise healthy. Those considering supplementation should establish a sound dietary basis before ensuring a balance in the foods consumed and maintaining sound hydration practices. Supplementation is unlikely to produce the desired results without an appropriate training stimulus. In order to supplement correctly, it is recommended that an athlete follow a traditional loading/maintenance programme with Cr ingestion best taken after training. Figure 10 highlights some of the key points raised in this article.

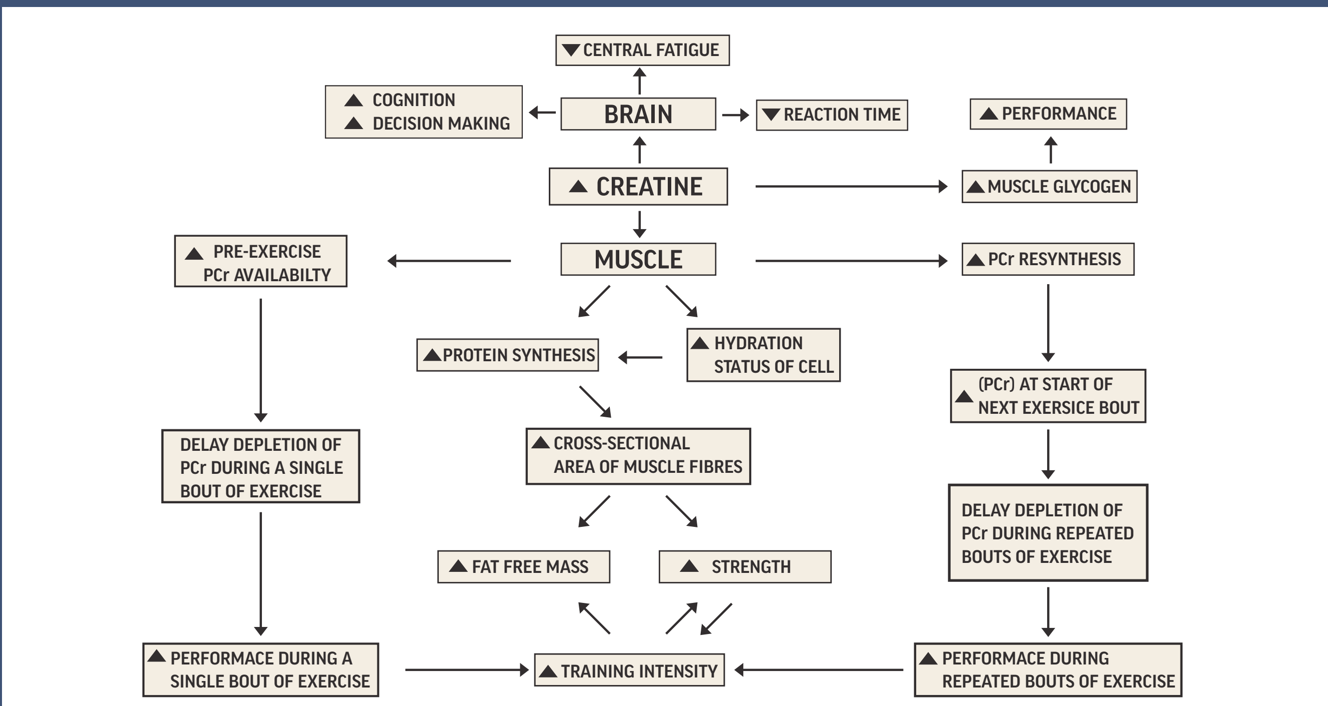

Figure 10. Schema of some likely effects of creatine supplementation on muscle and brain.

Author bio

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Don is an emeritus professor of Sports Nutrition at Liverpool John Moores University, which is a testimony to his many publications on the subject in journals and books as well as his presentations at scientific and coaching conferences. He has been research-active since 1980 in the fields of carbohydrate and fat metabolism, nutritional supplements, and applied aspects of sports nutrition. A consequence of the work undertaken has resulted in two fellowships being awarded i.e. FBASES and FECSS.

Don has been nutritional consultant with a number of Premiership and Championship football clubs as well as with Sale Sharks RUFC and Northampton Saints RUFC. His lecturing duties have resulted in many successful PhD, MSc and BSc students 'passing through his hands'. Although retired from full time duties at LJMU in 2010, Don has kept up his academic duties by lecturing to final year students and on the MSc programmes at LJMU, and the MSc programmes at the University of Chester and UCLAN.

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