MUSCLE METABOLISM AND FATIGUE DURING SPRINT EXERCISE: EFFECTS OF CREATINE SUPPLEMENTATION

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Abstract The aim of this paper was to examine muscle metabolism and fatigue during sprint exercise and also to critically evaluate the evidence regarding the efficacy of Cr supplementation in improving performance and reducing fatigue during one bout and repeated bouts of sprint exercise. Although glycolysis provides more than 50% of total energy supply during a single sprint, its contribution is reduced significantly and may drop to zero when sprints are repeated. Thus in this case, muscle relies exclusively on phosphocreatine (PCr) degradation and aerobic metabolism. Fatigue is shown to be related more to energy deficiency and performance recovery during repeated sprints follows closely the resynthesis of PCr. Due to the important role of PCr on muscle metabolism, an increase of PCr and creatine (Cr) content following oral Cr supplementation has been shown to be beneficial for performance. The effect of Cr supplementation on single sprint performance is small (around 5%) and not always present. A more substantial improvement in performance (around 10%) is demonstrated during repeated sprints, especially during the last repetitions. Although, Cr supplementation has not always proved to be beneficial for performance enhancement, even a small improvement may be important for competitive athletes. Research is needed to investigate and substantiate the effects of combining Cr supplementation with long term training on single and repeated sprints performance.

Key words: Phosphocreatine, anaerobic metabolism, energy supply, high intensity exercise

INTRODUCTION

Many people participate, at the recreational as well as at the competitive level, in multiple-sprint sports (such as soccer, tennis, basketball). These multiple-sprint sports involve a mixture of brief periods of exercise of maximum intensity followed by recovery periods of rest or light activity, and may last around 90 minutes. Recent studies have shown that not only anaerobic but also aerobic metabolism contributes significantly to energy supply during this type of exercise. Fatigue during this type of exercise has been related to energy availability, with phosphocreatine (PCr) playing a key role in muscle metabolism and performance recovery. This is because it provides energy at very fast rates but also because it is rapidly resynthesized in the recovery intervals separating bouts of intense exercise.

One way to improve performance during single and multiple sprint exercise activities is to increase energy availability. The observation that this is possible by oral Creatine (Cr) supplementation has made Cr a very popular supplement in sports. A large number of studies have shown that Cr supplementation results in an increased muscle total Cr content and muscle mass and also improves various aspects of strength and power performance. The greatest benefit of an enhanced muscle Cr and PCr content is the ability to repeat bouts of intense exercise separated by short recovery intervals, with less fatigue. This ability is paramount in games players as well as during training of many team and individual sports that involve

sprinting. Since Cr use is not prohibited in sports, many athletes consume Cr containing supplements during intense training periods as well as before major competitions. However, the evidence regarding performance improvement during single and repeated sprint exercise is conflicting.

Therefore, the aim of this paper is dual: Firstly, to examine muscle metabolism and fatigue during sprint exercise and secondly, to critically evaluate the evidence regarding the efficacy of Cr supplementation in improving performance and reducing fatigue during one bout and repeated bouts of sprint exercise.

MUSCLE METABOLISM DURING SPRINT EXERCISE

ENERGY SUPPLY DURING SPRINT EXERCISE

For the successful completion of any physical task, chemical energy must be efficiently converted into mechanical energy, at rates appropriate to the muscles' needs [56]. During a maximal 30 s sprint, where the energy demands are more than 2.5 times greater than the aerobic power (VO2max) can supply [123], the muscle cell is dependent on the energy provision systems that result in the greatest rates of adenosine-5-triphosphate (ATP) resynthesis, namely the creatine kinase/phosphocreatine system (CK/PCr) and anaerobic glycolysis. It has been estimated that these energy systems can resynthesise ATP at a maximum rate of ~8.6 (CK/PCr) and ~6.0 (anaerobic glycolysis) mmol.kg dry muscle-1.s-1, and reach this power in <1 s and 5 s, respectively [92]. The estimated ATP utilisation rate from anaerobic sources during a 30 s treadmill sprint is around 6.1-6.3 mmol.kg dry muscle-1.s-1 [22, 80]. When the duration of the sprint is shorter, the anaerobic ATP utilisation rate can be as high as ~15 mmol.kg dry muscle-1.s-1 (6 s cycle ergometer sprint) [38]. When 6-30 s sprints are repeated, there is a considerable decrease in anaerobic glycolysis and the muscle relies almost exclusively on PCr and aerobic metabolism [11, 13, 38]. Therefore, it can be argued that sprint exercise requires probably the highest rates of energy supply.

ATP RESYNTHESIS FROM PCR DEGRADATION

From all the processes in the cell that are used to regenerate ATP the creatine kinase reaction is the most powerful [92]:

$$PCr + ADP + H^+ \leftrightarrow ATP + Cr$$
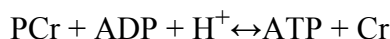
The muscle content of phosphocreatine (PCr) is 3-4 times higher than that of ATP. The activity of creatine kinase is higher than that of ATPase, which means that significant decreases in /ATP/ are seen only when PCr is broken down to 60% of the resting value or more [59]. During a 30 s bout of maximal exercise, PCr falls to near zero levels [79].

The creatine kinase reaction functions to buffer ATP to ADP ratio and has been considered to act as a stabiliser of intracellular adenylate gradients. It functions as a low-threshold ADP sensor (low K_m of CK for ADP) and plays a critical role in preventing a build-up of ADP, especially during transient periods of high energy utilisation [119]. An increase in free ADP may impair the function of the ATPases by product inhibition [24]. Furthermore, by maintaining the ATP/ADP ratio high in the vicinity of an ATPase, creatine kinase increases the thermodynamic efficiency ('free energy') of ATP hydrolysis. The same regulatory and thermodynamic aspects may also hold true for CK at the energy-producing side, where the enzyme is coupled to the ATP-generating systems (e.g. oxidative phosphorylation). In this case CK would be minimizing the free energy required for ATP synthesis.

An important feature of the CK/PCr system is that creatine kinase is expressed as four tissue-specific subunits: two 'cytosolic' forms, muscle-CK and brain-CK, and two mitochondrial-CK isoforms. These form three 'cytosolic' and two mitochondrial isoenzymes [119]. The 'cytosolic' CK isoenzymes are functionally coupled with the ATP requiring sites, by being located very close to the 3 different ATPases [90]. The mitochondrial isoenzymes have been suggested to play a special role. Bessman and Geiger [8], have proposed that PCr and creatine (Cr) function as a "shuttle" for the transport of high-energy phosphates between the mitochondrial and myofibrillar CK isoenzymes. Tracer studies have shown that mitochondrially generated ATP has preferential access to the reactive site of mitochondrial CK [33]. Similarly, a significant fraction of cytoplasmic CK is bound to the M-line of myofibrills, and PCr is reported to

be a preferred substrate for myofibrillar phosphate liberation compared with externally supplied ATP itself [115].

The participation of hydrogen ions (H^+) in the creatine kinase reaction has an important physiological consequence: Breakdown of PCr will absorb H^+ and this will increase the intracellular pH during the first seconds of maximal contraction. It is thought that this alkalinization will facilitate activation of phosphofructokinase (PFK) and phosphorylase system ('key' enzymes) and accelerate glycolysis.

PCr can supply energy at very high rates during the first few seconds of intense exercise. However, the limited muscle content of PCr can not support these rapid rates for a long period. Therefore, the glycolytic pathway is activated almost immediately after the start of intense contractions [57, 95]. The link between phosphocreatine breakdown and glycogen utilisation in the muscle, is thought to be the inorganic phosphate (Pi) liberated during ATP-PCr degradation [21].

GLYCOLYTIC ENERGY SUPPLY DURING SPRINT EXERCISE

In comparison with the high energy phosphates (ATP, PCr), the content of glycogen in the muscle is larger (300-400 mmol/kg dry muscle) [9, 11, 13]. Muscle glycogen and glucose can be utilised in the glycolytic pathway and rephosphorylate ADP at high rates. The percent contribution of anaerobic glycolysis to total anaerobic ATP turnover during a 30 s sprint is about 50% when the aerobic contribution is also taken into account [11]. This is reduced to about 36% when a 30 s sprint is repeated after a 4 min interval [11]. The decrease in glycolysis during repeated sprint exercise is related with a decreased activity of key glycolytic enzymes, mainly glycogen phosphorylase and phosphofructokinase (PFK), due to muscle acidosis [107]. Interestingly, Gaitanos et al. [37] found that glycolytic energy supply dropped to zero in the last bout of ten 6 s sprints separated by 30 s of recovery.

The glycogen stores in skeletal muscle are reduced only by a small percentage (20-30%) after a 30 s sprint bout. Although it is unlikely that glycogen availability can limit exercise performance during short term sprinting, analysis of metabolites in single fibers following electrical stimulation or short lasting very intense exercise, has shown a ~2-fold greater decrease in glycogen in the fast, compared with the slow twitch fibers [44, 45, 100, 118].

CHANGES IN ACID-BASE BALANCE DURING SPRINT EXERCISE

Lactate is the end product of anaerobic glycolysis. Lactate in the muscle is immediately dissociated into La^- ions and H^+ ions. Since pH is the negative logarithm of the hydrogen ion concentration, muscle pH is reduced when lactate is produced. Muscle lactate concentration during sprint exercise is increased up to a maximum of about 130-140 mmol/kg dry muscle [9, 11, 13, 38]. This is accompanied by a reduction of muscle pH from about 7.0 to a 6.6-6.4 [9, 11, 13, 103], despite of the muscles ability to buffer changes in H^+ [82]. Decreases in muscle pH play a significant role in muscle fatigue by several mechanisms which are reported below.

OXIDATIVE ENERGY SUPPLY DURING SPRINT EXERCISE

Numerous studies have shown that the contribution of aerobic metabolism to energy release increases with the duration of exercise [74]. The mean power output during the "Wingate test" (30 s all out sprint cycling), was assumed to represent the "anaerobic capacity", i.e. the maximum amount of anaerobic energy release during exercise [5]. However, studies have shown that aerobic metabolism can provide 18% to 40% of total energy supply during a 30 s sprint [11, 13, 64, 74]. The value of 40% for aerobic contribution during a 30 s exercise bout reported by Medbo and Tabata [74] is probably an overestimation for sprinting because it was calculated using the method of oxygen deficit. Calculation of aerobic energy contribution from muscle biopsy and oxygen uptake data provides values of 29% for a 30 s sprint and 14% for a 10 s sprint [11, 13]. If a 30s sprint is repeated after a 4 min rest interval, aerobic contribution to energy supply increases to an average of 43%, which becomes higher towards the end of the sprint [11].

The increased contribution of aerobic energy to the total ATP turnover as sprint exercise is repeated has also been shown with repeated sprints short duration (<30 s). Gaitanos et al. [38] reported that during a protocol of ten 6 s sprints separated by 30 s rest intervals, there was a decrease of 70% of anaerobic energy supply, but only a 27% drop in mean power output in sprint 10 compared to sprint 1. This mismatch between external work and metabolism was explained as an increased contribution of aerobic metabolism.

The enhanced aerobic contribution to energy turnover during repeated sprint exercise has been recently demonstrated indirectly by Burgomaster et al. [17] who showed that only six sessions of repeated sprint exercise (four to six 30 s sprints with 4 min rest per session) increased muscle oxidative potential and doubled endurance capacity in young active individuals.

RECOVERY OF MUSCLE METABOLISM AFTER SPRINT EXERCISE

Immediately after high intensity exercise, PCr content in the working muscles is very low. Phosphocreatine resynthesis is a rapid process during recovery from intense exercise. The time course of PCr resynthesis after exhaustive dynamic exercise (8.7 min cycling at 60 revs.min^{-1}) and isometric knee extension (40-55 s at 66% of maximum voluntary force) has been examined by Harris et al. [49], who took repeated biopsy samples during recovery. The data have been modelled using a two component exponential equation (fast and a slow recovery component), allowing the calculation of half-times, time-constants and rate constants for PCr resynthesis. While no difference was found between the half time of the 'fast' component of PCr resynthesis after isometric and dynamic exercise (about 30 s), the amount of PCr resynthesised after 2 and 4 min of recovery was lower following isometric exercise.

The differences in PCr resynthesis between isometric and dynamic exercise has been examined by Nevill et al. [78] who fitted PCr recovery data from isometric electrically stimulated contractions and following a 30 s sprint. In the isometric study, PCr concentrations rose during the recovery phase to a level above that observed at rest. In the sprint study PCr recovered monotonically to resting concentrations. The second exponential term in the double-exponential model was found to make a significant additional contribution to the quality of fit in both studies. As shown by Bogdanis et al. [9] only about 85.5 ± 3.5% of the resting PCr was resynthesized after 6 min of rest following the completion of a 30 s sprint, while half time of PCr resynthesis was more than double (56 s) compared to the values reported for isometric and dynamic exercise of longer duration. These data show that PCr resynthesis is slow after sprint exercise, possibly due to pooling of the blood in the legs.

It has been suggested that the initial fast phase of PCr resynthesis is limited by the availability of oxygen, whereas the subsequent slow phase is limited by the hydrogen ion transport out of the muscle [93]. An oxygen dependent mechanism for the initial PCr restoration was hypothesised, which was linked to the activity of the mitochondrial isoenzyme of creatine kinase. This demonstrated the significance of oxidative phosphorylation for PCr resynthesis. This evidence links the process of PCr resynthesis with muscle blood flow and oxygen supply. The importance of the circulation during recovery has been demonstrated by the finding that no PCr resynthesis occurred when blood flow to the leg muscles was occluded after fatiguing contractions [49, 50]. Also, the fact that active recovery results in a better peak power output restoration indicates the importance of blood flow during recovery [12]. An important consideration when examining the recovery of PCr following intense exercise is the difference in PCr resynthesis between the two major fiber types (fast and slow twitch). In a study by Tesch et al. [108], PCr was resynthesised to 50% (fast twitch) and 68% (slow twitch) of the resting level, 60 s after 30 maximal voluntary knee extensions. Similarly, PCr was higher in the slow twitch fibers 1 min after 83 s of electrical stimulation of the quadriceps at 20 Hz [101]. These differences between fibers were assumed to be related to the higher mitochondrial density and capillarization of the slow twitch fibers [101].

As discussed before, muscle pH drops to about 6.5 - 6.7 after repeated 30 s bouts of maximal sprint exercise [9, 11 104]. The recovery of muscle pH after intense exercise is a slow process, in comparison with PCr restoration. Allsop et al. [2], used a needle-tipped pH electrode which allowed monitoring of the changes in extracellular pH after a maximal 30 s sprint on a non-motorised treadmill. Muscle pH decreased from 7.17 ± 0.01 at rest to 6.57 ± 0.04 immediately after the sprint. No significant recovery occurred in muscle pH for 10 min, after which muscle pH increased to 7.03 ± 0.03 by 30 min. The effect of low pH on anaerobic glycolysis reduces glycolytic energy supply if a subsequent sprint is attempted after a short interval following a 30 s sprint [11]. Therefore, the slow recovery of muscle pH results in a greater dependence on aerobic metabolism and PCr when sprint exercise is repeated.

METABOLIC ASPECTS OF FATIGUE DURING SPRINT EXERCISE

Following short-term intense exercise, fatigued muscle exhibits impaired contractile performance, characterised by decreases in the maximal contraction velocity, peak tension, and rate of ATP hydrolysis. The basic mechanisms and the physiological sites involved in fatigue are complex. Edwards [32] defined fatigue as "the failure to maintain the required or expected power output or force", and distinguished between central and peripheral fatigue. Central fatigue was attributed to impaired motivation (e.g. pain or perception of excessive effort) and reflex drive, and had its origin in the central nervous system. Peripheral fatigue refers to impaired activation/excitation of motor units, energy supply, and actin-myosin cross bridge coupling. Edwards [32] finally suggested that fatigue is local in origin, with the brain simply modifying local events. It has been suggested that most human muscles can be fully activated by voluntary effort, but maximum force can only be sustained by highly motivated and experienced subjects in the presence of visual feedback [62].

Much more attention has been directed towards the metabolic basis of fatigue. The decline of contractile force of skeletal muscle that occurs with fatigue is associated with a decrease in intracellular levels of PCr and ATP, an increase in inorganic phosphate (Pi) and its acidic fraction (H_2PO_4-), H^+, and ADP, and the consequent decrease in free energy available from ATP hydrolysis [40]. All of these changes have been suggested as possible fatigue-inducing agents [120].

Fatigue, in metabolic terms, may be termed the mismatch between ATP demand and ATP supply during exercise. During maximal exercise, PCr drops to near zero values and the products of the ATP hydrolysis (Pi, ADP, H^+) accumulate. ^{31}P-MRS studies have shown that the effects of inorganic phosphate on force production are potentiated when a decrease in muscle pH occurs due to high rates of anaerobic metabolism [122]. This is because the pK of phosphate is about 6.8 and a shift in pH changes the proportions of the monobasic (H_2PO_4-) and dibasic species (HPO_4^{2-}). Wilson et al. [122] argued that accumulation of $H_2PO_4^-$ was the main cause of fatigue. Clearly there is an effect of Pi and $H_2PO_4^-$ on force generation, but it is not the only factor to induce fatigue.

One of the characteristic features of skeletal muscle fatigued by high force contractions is a slowing of the rate of relaxation. Two mechanisms can explain slowing of relaxation: (i) a reduced rate of cross bridge cycling in the fatigued state, due to a reduction in ATP or increase in ADP and (ii) reduced rates of Ca^{2+} reuptake by the sarcoplasmic reticulum ATPase [37, 120].

Potassium (K^+) has a vital role in muscle function. The excitability of muscle membrane is dependent on the membrane potential, which, in turn, is dependent mainly on the K^+ gradients across the membrane. Consequently, the rise in extracellular potassium seen during high intensity exercise, will eventually cause a depolarisation block, and may be related to fatigue in that type of exercise [117]. The loss of intracellular K^+ has been attributed to an impairment of the function of the Na^+-K^+ pumps. The ensuing potassium accumulation in the t-tubules may also be related to a 'local' energy deficiency at the site of Na^+-K^+ ATPase [72].

The involvement of hydrogen ions in fatigue has been demonstrated in numerous studies. H^+ accumulation is linked with a number of effects such as: decrease in the rate of glycolysis, product inhibition of all three ATPases (myosin, Ca^{2+} reuptake, Na^+-K^+), competition with Ca Ca^{2+} for the binding sites of troponin C, reduction of Ca Ca^{2+} release from the sarcoplasmic reticulum, reduction of sensitivity of the contractile mechanism to Ca^{2+} [24, 120]. However, several studies examining recovery of muscle force and power following high intensity exercise, have clearly shown that the contractile mechanism is not impaired so much by acidosis, while recovery of force and power output follows a time course similar to that of PCr resynthesis [9, 11, 13, 94].

As noted above, the ATP utilising processes involved in muscular contraction are catalysed by myosin ATPase, Ca^{2+} transporting ATPase, and Na^+-K^+ ATPase . For power generation (which involves both force and velocity), the function of all the ATPases is important. The discovery of functionally coupled processes in muscle cells for all three ATPases, has provided a new insight into the causes of fatigue. Several studies have shown that creatine kinase isoenzymes are localised at the myofibrillar M-band, the sarcoplasmic reticulum and the sarcolemma membrane, and are important regulators of relaxation and tension development by preventing product accumulation and providing ATP in the immediate vicinity of each ATPase [119]. PCr availability at the site of each ATPase, may be of greater importance when the

system is maximally and repeatedly stressed. Since glycolytic rate is significantly reduced during a repeated sprint. The rapid resynthesis during recovery provides readily available energy for rapid use during the first seconds of a repeated sprint and this explains the close relationship between power output recovery and PCr resynthesis [9, 11].

ORAL CREATINE SUPPLEMENTATION

BIOSYNTHESIS
Cr is a nitrogenous amino acid compound that took its name by the Greek word "kreas" (meat). Although it was discovered in the 1830s, Cr metabolism in human muscle was explored relatively recently with the aid of the muscle biopsy technique and the nuclear magnetic resonance spectroscopy [71]. Cr is stored mainly (95%) in skeletal muscle in the form of phosphocreatine (PCr) and Cr. The average concentration of PCr and Cr in human skeletal muscle is approximately 75 and 50 mol/kg dry muscle, respectively [9, 11, 52], while total Cr is slightly lower in vegetarians [18, 114]. The dietary source of Cr is meat and fish but it can also be synthesized mainly in the liver as well as in pancreas and kidney, by the precursor aminoacids arginine, glycine and methionine [124]. Normally, Cr degradation to creatinine with subsequent excretion in urine is about 2 g/day. This is replaced by ingestion of food containing 1-2 g of creatine (meat and fish) and/or by endogenous synthesis of creatine that may amount to 1-2 g/day (*Figure 1*). Due to the capacity of the body to synthesize Cr endogenously, total Cr pool remains constant even if no meat or fish is consumed in the diet. It must be noted that red meat contains 4-5 g Cr per kg, while Cr content in herring is approximately 10 g per kg [48, 51].
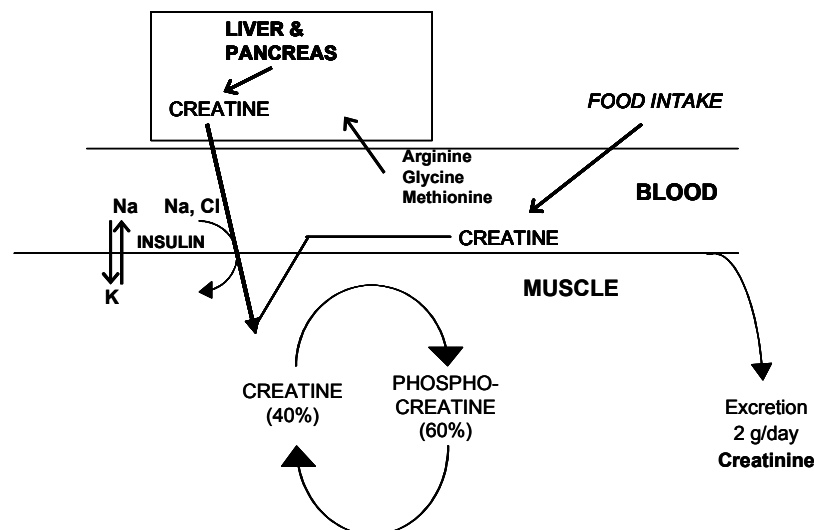
Figure 1. Creatine metabolism in the human body.

CREATINE TRANSPORT INTO MUSCLE
Creatine is transported via the blood and enters muscle cells against a very large concentration gradient, by means of a Na^+ and Cl^- dependent Cr transporter protein [15, 99, 119]. Plasma Cr levels in meat eaters range from 50-100 μmol/L [52], while the Cr transport mechanism exhibits an apparent Michaelis constant (K_m) for Cr of 15-30 μmol/L. Thus, normal plasma Cr ranges are adequate for transport in the muscle. Although it is well established that fast twitch muscle fibers (type II) have a higher total Cr content than slow-twitch (type I) fibers [19, 100], type I fibers have greater Cr transporter protein content and higher Cr uptake ability [16]. This may indicate that individuals with a higher percentage of slow (type I) fibers respond better to Cr supplementation than those with a high percentage of fast twitch fibers. Also, since Cr uptake is

regulated by pre-supplementation total Cr muscle content, individuals with low initial total Cr such as vegetarians, respond better to Cr supplementation [6, 18].

Recent findings in healthy humans provide evidence that long term Cr supplementation (>2-3 months) may result in a decline of muscle total Cr from its peak supplementation level, even though supplementation is continued [29, 545, 113, 116]. Although the mechanism for this habituation to chronic creatine exposure is poorly understood, there is evidence of downregulation of the expression of the Cr transporter isoforms [47] and/or inhibition of the transporter activity [70]. However, the importance of the Cr transporter for regulating muscle Cr content needs further research, since, as mentioned above, Cr content is higher in the fast twitch fibers that have the lowest content of Cr transporter protein.

SUPPLEMENTATION SCHEMES

The most common scheme for Cr supplementation is 20 g/ day (in four 5 g doses) for 4-6 days [52]. This dose it termed as Cr "loading" and can also be prescribed according to body mass (approximately 0.25 g/kg body mass per day). Ingestion of a 5 g dose results in an increase of serum Cr from 50-100 µmol/L to a peak of 800 µmol/L in about 1 hour. Above-resting serum Cr concentrations remain for about 6 hours after ingestion. The initial [52] as well as subsequent Cr supplementation studies [58] showed that most of the daily Cr dose is retained on day 1 of supplementation, while there is a decreasing pattern of Cr uptake in the next 4-5 days. In fact, only a very small percentage of the daily dose is retained in day 5, irrespective of the magnitude of the dose (*Figure 2*). A limit of 160 mmol/kg dry muscle has been demonstrated in many studies [52, 58] and when this is reached, further supplementation leads only to excretion of Cr and creatinine in the urine. If Cr supplementation is stopped after loading, total Cr in the muscle returns to baseline values in about 4 weeks [58]. However, total muscle Cr can be maintained for at least 4-6 weeks after loading by the ingestion of small daily Cr doses of 2-5 g [58, 85].
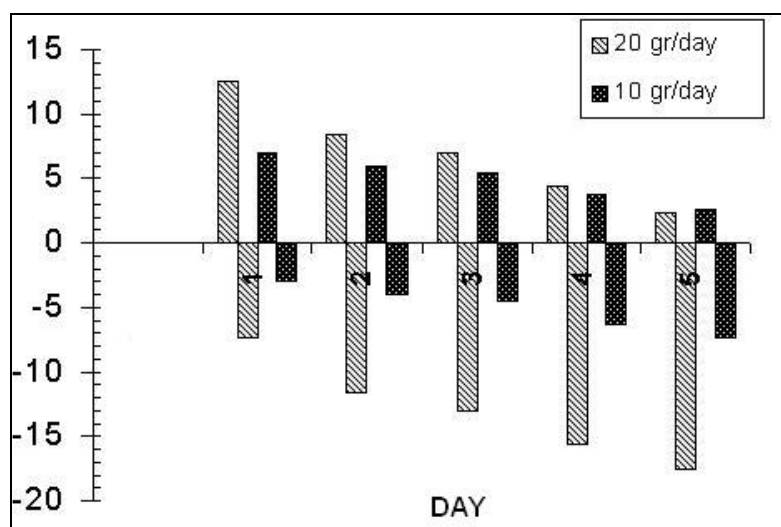
Figure 2. Creatine retention and excretion during 5 days of supplementation using two different doses (10 and 20 g of Cr per day). *Bogdanis et al. unpublished data*.

A more conservative approach to Cr supplementation is to use small doses and avoid the Cr loading period. The efficacy of this scheme was first shown by Hultman et al. [58], who demonstrated that a dose of 3 g/day resulted in an increase in total Cr to levels similar to a loading protocol after 28 days of supplementation. This approach decreases both the daily and the total amount of Cr ingested, thus reducing the possible stress of a high Cr load on the liver and kidney. Although it has been suggested that liver and renal function are not impaired by the usual Cr supplementation schemes [84], it is appealing to have the same effect with 10-17% of the daily dose (2-3 instead of 20 g/day). More recent studies have used small doses of Cr (6-7 g/day) for 6-7 days and observed some [55] or no effect [112] on high intensity exercise

performance. Perhaps more days of small dose supplementation are needed to have a considerable effect on performance.

In an attempt to maximize Cr uptake by the muscles, Harris et al. [52] combined Cr supplementation with 1 hour of submaximal one-leg exercise each day. The increase in muscle blood flow was put forward to explain the higher Cr concentration in the muscles of the exercise leg. Modulation of the Cr transporter by exercise may also be another explanation for these findings [87]. However, prolonged exercise may also play a negative role in Cr uptake by the muscles. It is well accepted that endurance exercise blunts the CHO mediated insulin release. Since Cr transport is also enhanced by insulin stimulation, prolonged exercise should be avoided during Cr supplementation if Cr retention is to be maximized [87].

The modulation of Cr transport by insulin has been exploited as a means to increase Cr retention during supplementation. Several studies have shown that combining Cr with carbohydrate uptake, leads to a greater Cr retention [41, 87]. However, since a large increase of insulin (>100 mU/L) [105], is required in order to have a significant effect on Cr uptake, a large consumption of carbohydrate is required (about 500 g of a 18.5% simple carbohydrate drink with each 5 g Cr dose). The effect of insulin to increase muscle Cr uptake has been mainly attributed to stimulation of Na+-K+ ATPase function, allowing Cr to enter the muscle against a large concentration gradient [105]. However, in practical terms, it is important to note that the stimulating effect of insulin on Cr disposal was diminished within the initial 24 h of supplementation [105].

There is evidence that total Cr content of the muscle is decreased in prolonged ingestion, irrespective of efforts to maintain it. A suggestion to overcome this problem may be intermittent supplementation. Based on the evidence from the studies presented in so far, supplementation may be interrupted for about 2 weeks every 4-6 weeks and this may result in stable total Cr over a long period of time in the muscle [29]. However, the effects of intermittent Cr supplementation remain to be studied.

EFFECTS ON PHOSPHOCREATINE AVAILABILITY AND PCR RESYNTHESIS

It has been well established that Cr supplementation results to an increase in TCr and PCr into the muscle fibers [4]. However the increase in total Cr in the muscle does not occur to the same extent in all the participants in the various studies. An average increase of PCr following Cr supplementation is 15%, ranging from 0 to 20% [7, 75], and this may provide an ergogenic effect, by maintaining a high ATP synthesis rate from PCr for a slightly longer duration, during a single bout of sprint exercise. Based on the contribution of PCr on energy supply during a 10 s and a 30 s bout of sprint exercise, a possible 10-20% increase in muscle PCr is expected to improve performance by 3-6% and 2-4% respectively.

Probably the most beneficial effect of Cr supplementation may be during repeated bouts of intense exercise. This is explained by a faster PCr resynthesis during the interval separating the exercise bouts. Greenhaff et al. [42] examined PCr resynthesis after intense electrically evoked isometric contraction, taking muscle biopsies at 0, 20, 60 and 120 s of recovery. Elevation of total Cr following supplementation resulted in a higher PCr resynthesis only after 120 s of recovery, while there was no effect of the increased Cr content in PCr resynthesis after 20 or 60 s or rest. They explained this observation by referring the kinetics of the backward CK reaction (PCr resynthesis). The in vitro Michaelis constant (K_m) values of CK for Cr is close to 60 mmol/kg dry muscle. It is known that muscle free Cr can range in concentration from about 50 mmol/kg dry muscle at rest to 120 mmol/kg dry muscle after maximal exercise. Thus, during the initial stages of recovery from maximal exercise, when the rate of mitochondrial ADP rephosphorylation to ATP will be at its highest, it is unlikely that the rate of PCr resynthesis will be dependent on the availability of free Cr, because its concentration will be far in excess of the Km value. However, as PCr resynthesis continues and as the muscle free Cr concentration declines towards 60 mmol/l, it is suggested that free Cr concentration may then begin to be a determinant of the rate of PCr resynthesis. The increase of total Cr following Cr loading kept Cr concentration during recovery well above this Km value 120 s into recovery, while Cr dropped to lower levels during the corresponding time point in the control condition. The implications of this fact are of great importance on the choice of resting interval when sprints are repeated. According to the above study, the effects of Cr supplementation on PCr resynthesis and subsequent muscle performance would not be evident if an interval less than 120 s is used. On the other hand, if the interval is extended to more than 6 min, PCr will be resynthesized to

almost resting levels, thus masking the possible effects of Cr supplementation [23]. Nonetheless, the optimal recovery interval for PCr resynthesis during multiple sprints following Cr supplementation has yet to be determined.

CHANGES IN BODY/MUSCLE MASS FOLLOWING CR SUPPLEMENTATION: IMPACT ON SPRINT RUNNING PERFORMANCE

A typical Cr loading protocol (containing 20 g of Cr per day, for 5 days) results to a 20% (range: 0-35%) increase in TCr into skeletal muscles and a corresponding increase in PCr ranging between 6-20% [35, 73, 85, 121]. This is usually [31, 36, 42, 63, 65, 116] but not always [26, 46, 68, 96, 107] accompanied by a body mass gain between 1 and 2 Kg, which corresponds to 1-2.5% of body mass. The acute increase of body mass during the first days of supplementation is mostly accounted for by increases in intracellular water since increased concentration of free Cr in the cells induces water retention [36]. The notion that water is retained to the body is reinforced by the finding of Hultman et al. [58] that during the 3 first days of Cr supplementation less urine is excreted. The longer term increase in body mass is attributed less to a body fat increase and primarily to fat free mass development [31, 39, 46, 66, 116]. This occurs mostly in the case where Cr supplementation is accompanied with resistance training. Increases in total Cr may result in higher muscle mass development not only by an effect on protein synthesis and degradation, but also by improving the quality of training [36, 66, 106, 113, 116]. In the study by Volek et al. [120] including a 12-week resistance training program, the group that consumed Cr demonstrated a remarkable increase in cross-sectional area of all types of muscle fibers (type I: 35%, type IIa: 36% and type IIab: 35%) in contrast with the smaller increase in the control group (11%, 15% and 6%, respectively).

Although the increase in body mass may be desirable in some sports (e.g. body building), there is concern about a negative effect of the extra weight on performance in tasks where body mass has to be moved (e.g. jumping, running). In these cases, the increase in force and power in relation to body mass must be examined. An increase in body mass may be a possible explanation for the absence of an ergogenic effect of Cr in some studies involving running [e.g. 28].

EFFECT OF CR SUPPLEMENTATION ON SINGLE SPRINT PERFORMANCE

Numerous studies conducted during the last decade have examined the ergogenic effect of Cr supplementation, reporting conflicting results (Table 1). In a single sprint, performance enhancement after Cr supplementation is expected due to increased availability of PCr into the muscle fibers before the sprint [4, 19, 43, 67, 73]. However, as reported earlier, the increase in PCr after Cr loading is about 10-20% and thus the expected improvement in performance is relatively small. This reduces the possibilities that improved performance during a single sprint reaches statistical significance and therefore only a few studies have explored the effect of Cr supplementation on a single maximal bout alone. However, most studies using a series of repeated bouts of sprint exercise have referred to the ergogenic or not effect of Cr supplementation during the first bout, providing information concerning single sprint performance improvement. This has practical value for some sports that involve only one maximal effort (e.g. track sprinting, sprint swimming etc).

Theoretically, peak speed or peak power output are not expected to increase after Cr supplementation because the maximal rate of PCr breakdown can not be affected by increased PCr resynthesis. Therefore, the ergogenic effect of Cr supplementation in a single sprint will be a result of a better maintenance of a high power output towards the end of the sprint. Thus, total work is expected to increase and power or speed decline during the sprint may be reduced following Cr supplementation. In a placebo controlled study on elite sprinters [97], 100 m time on the track was improved after Cr but not after placebo intake (Placebo: 11.74 ± 0.35 vs. 11.76 ± 0.35, Cr: 11.68 ± 0.27 vs. 11.59 ± 0.31, $P<0.02$) with this difference being the result of a faster time during the last 40 m of the 100 m race. Furthermore, total work in a 10 s cycling sprint was improved in elite athletes of various sports who were supplemented with Cr [125]. Using 31-phosphorus MRS Kurosawa et al. [67] observed an increase in the average anaerobic ATP resynthesis rate through PCr degradation and anaerobic glycolysis after Cr supplementation (0.97 ± 0.16 to 1.33 ± 0.27 mmol/kg wet muscle weight/ sec, $P<0.05$), during a 10 s maximal hand grip exercise. PCr muscle content increased 11.5 ± 4.6% in the Cr supplemented group and all participants in this group demonstrated an improvement in mean power output during the 10s maximal exercise (15.1 ± 3.8%, $P<0.05$).

A positive effect of Cr loading that may influence sprint exercise performance is the shortening of relaxation time. This has been observed during brief maximal isometric contractions [111] and would suggest that Cr supplementation may also improve and/or prevent the drop in the rate of contraction/relaxation cycles during a sprint.

Although some studies have successfully demonstrated the ergogenic aid of Cr supplementation on a single bout, contradicting results have been reported in some studies [25, 28, 30, 98]. In a double-blind study, Cooke et al. [25] reported no effect of Cr supplementation on two 15s cycling sprints separated by 20 min of rest. This rest interval is so long, that these sprints may be considered as single and not repeated sprints. In addition, Snow et al. [98] examined muscle metabolism during one bout of maximal cycling exercise after Cr supplementation. Although no effect of Cr supplementation on performance was observed, researchers reported that very low Cr retention was achieved, and the low increase in PCr could not result in a statistically significant improvement in performance. However, the positive relationship observed between the percent change in peak power output during sprinting and the percent increase in total Cr after supplementation, indicated that Cr supplementation could have improved performance had the increase in PCr been adequate [98]. However, it must be noted that in the case of elite athletes, where a slight improvement in performance is decisive, even a small positive effect of Cr loading may be beneficial.

In a study involving rowers, time in 1000 m of rowing was improved by 2.3 s (from 211.0 ± 21.5 to 208.7 ± 21.8) after 5 days of Cr intake, with almost all rowers (16 of the 19) that consumed Cr demonstrating faster race time. However this improvement was not statistically significant [91]. Similarly, no ergogenic effects of Cr supplementation have been reported for swimmers performing 25, 50 and 100 m [76] and runners performing a 700 m race [107].

Unfortunately, no study has examined the effects of long-term Cr loading combined with training on sprint performance. Although this topic deserves further research, it can be hypothesized that an increase in PCr content will also act indirectly by improving the quality of training. Furthermore, the possible increase in muscle mass and fiber area after Cr supplementation and training may act independently to improve sprint performance.

EFFECT OF CR SUPPLEMENTATION ON MULTIPLE SPRINT PERFORMANCE

As reported in the previous chapter, the increased concentration of Cr and PCr in the muscles after Cr supplementation may be beneficial for athletes training or competing in sports including one maximal exercise bout. However, an ergogenic effect of Cr supplementation is expected to be more evident when sprinting bouts are repeated with short rest intervals, where performance is closely related with PCr restoration during recovery [9, 11].

Improved performance in repeated sprints has been reported in cycling [4, 10, 19, 61, 77, 81, 88, 125], running [27, 60, 97], or in specific maximal intermittent skills [89] (also see Table 1).

The ergogenic effect of Cr supplementation on cycling performance has been manifested by higher power output during a 10 s sprint that was performed 40 s after a series of five 6 s sprints interspersed with 30 s of recovery [4]. In a protocol of repeated cycling sprints with longer recovery intervals (6-10 s sprints separated by 60 s of passive rest), a higher peak power output in sprints 2 to 6 has been reported after Cr supplementation [125]. Moreover, remarkable increases in power output during cycling sprints and a decrease in total time for performing six repeated skating sprints was observed after 5 days of Cr loading and after 10 weeks of a maintenance dose in ice hockey players [61]. In particular, ten days after the baseline tests, and following Cr loading, average peak power output over the five 15 s sprints separated by 15 s of recovery increased from 1294 ± 311 to 1572 ± 462 W while a similar increase was found for mean power output (from 890 ± 172 to 1074 ± 241 W).

Positive effects of Cr supplementation have also been reported in sprints of longer duration [19, 20, 81] (also see Table 1). In a recent study, a significant ergogenic aid of Cr was apparent in five Wingate tests (30 s maximal cycling) with 2 min rest interval [81]. In particular, total mean power output was increased 7.6% (from 366 ± 65 W before supplementation, to 394 ± 67.1 W after supplementation), as a result of a higher mean power output in each sprint and especially in sprints 3 and 4.

Only a few studies have examined the effects of Cr supplementation on performance during sprint running (Table 1). Skare et al. [97] reported an improvement in repeated sprints (6 x 60 m) total time, after Cr supplementation in sprinters. Bogdanis et al. [10] examined power output and running distance in six 10 s sprints separated by 30 s of passive recovery on a non-

motorized treadmill. Although peak power in all sprints was not affected by Cr supplementation, mean power and sprint distance increased over the last two sprints only in the Cr group. Positive effects of Cr consumption have been demonstrated even when sport specific maximal intermittent skills are tested [61, 89]. For example, a 3.2 ± 0.8% higher improvement in performance during ten maximal sets of 2 repetitions of simulated positional play (each set interspersed with 30 s passive recovery) was evident for squash players that received Cr, in comparison with the placebo group [89]. Although, a disproportional body mass increase after Cr supplementation may theoretically prevent performance enhancement in sprint running, the improvement in both repeated sprints and agility tasks that has been reported in the literature shows that strength and power increase usually outbalance the negative effects of an increase in body weight in weight-bearing activities (Table 1).

The sprint duration may mask the ergogenic effect of Cr supplementation. In a study conducted by Izquierdo et al. [60], 19 male handball players were tested in various tests including maximal strength, jumping ability and repeated running sprints. Although time in 15 m sprints was not improved in the Cr supplemented group, a decrease in the time of the first 5 m of the sprints was observed in this group. Authors reported that the effect of Cr may be more evident in repeated bouts lasting 1-2 s (e.g. 5 m run), because during that time frame PCr degradation contributes mostly in energy supply [60].

In a study exploring the role of Cr supplementation in groups undergoing energy restriction in order to reduce body mass, increased Cr and PCr stores (15.6 and 15.1%, respectively) have been reported [88]. Apart from this increase, a tendency for improved total work and work capacity during ten 6s cycling sprints with 30s interval, was observed. The 3.8 ± 2.2% increase in total work (p = 0.058) and work capacity (p = 0.072), although not statistically significant, would probably be of importance in the case of competitive elite athletes. It may be speculated that Cr supplementation may prevent the drop in power output and the impairment in muscle function, reported during energy restriction in weight-categories athletes [86, 110].

Although many studies have proved the ergogenic aid of Cr supplementation, others, involving different types of exercise (cycling, running, specific skills) have failed to do so [1, 26, 28, 30, 35, 39, 65, 73, 83] (also see Table 1]. Many factors such as the type of exercise [68], the sprint and recovery duration, the supplementation protocol [55, 112], the interindividual differences (responders and non responders [69] or the method used for power output calculation [53] may be responsible for the confounding results reported. Besides, a faster rate of PCr resynthesis during recovery may occur only if a marked increase in TCr has been displayed after Cr supplementation [42].

In a study were muscle samples were taken before and after a Cr supplementation protocol, recreationally active males and females exhibited a significant 18.0 ± 3.6% increase in TCr (22.9 ± 4.2 mmol/kg dry muscle), which however was not accompanied by any increase in PCr or in cycling performance [73; see Table 1]. Furthermore, no benefit of Cr supplementation during 4-20 s cycling sprints interspersed with 20 s of recovery was evident, although an elevation of TCr in the muscles of the triathletes tested was observed after supplementation [35].

In highly trained athletes performing either 6-40 m running sprints (with 30 or 120 s of recovery [28], or two Wingate tests (30 s cycling) separated by 4 min of active rest [30], no improvement in performance has been reported. However, the extent of the possible increase in TCr or PCr following supplementation was not measured. Similar failure to observe performance improvements have been reported for rugby players involving both cycling and running repeated sprints [1], while Pluim et al. [83] showed no ergogenic effect of Cr supplementation in the ability to perform running (20 m) or tennis specific performance indices that are maximally repeated with short intervals.

Finally, in contrast with the results of Jones et al. [61, Table 1] who demonstrated an increased performance of ice hockey players after Cr supplementation, Cornish et al. [26] failed to present any ergogenic effect of Cr intake in the ability of ice hockey players to repeat 10 s skating sprints with short rest interval (30 s) on a skating treadmill, until exhaustion. No increase in the total sprinting time to exhaustion or in isokinetic trials was observed in the tests after 5 days of Cr supplementation [26].

PRACTICAL APPLICATIONS

Since sports involving single and multiple sprints are very popular, information regarding the causes of fatigue may be extremely useful to coaches and practitioners. In this paper, the importance of PCr for high intensity sprint performance has been highlighted and explained. During repeated sprint exercise, the interval between bouts should be adequate to ensure PCr resynthesis if peak and mean power is to be reproduced. Contrary to the common practice and belief, it may take much longer than the usual 3 min for complete PCr recovery. Coaches must know that when sprints are repeated, aerobic metabolism becomes more and more important while lactate production may be completely blocked. In this case, while the intention of the coach is to improve anaerobic metabolism and lactate production, repeated sprint training may improve aerobic metabolism instead.

Due to the importance of PCr during repeated sprint exercise, Cr supplementation has gained popularity in recent years. Coaches and athletes should expect a small improvement in single sprints and a greater improvement in multiple sprints. However, it should be noted that the positive effects of Cr supplementation are not evident to all people. One indication that Cr supplementation works for an individual may be the increase in body mass during the first 5 days of a loading phase. If this does not occur, possibly Cr supplementation will not work for this individual.

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Table 1. Selected studies on the effect of creatine (Cr) supplementation on single and multiple sprint performance.

Reference	Participants	Dosage (g X times, days)	Tests	Results
Ahmun et al. 2005	rugby players	20 g/day, 5 days	10 X 40 m running sprints 10 X 6 s cycling sprints	• no effect for peak or minimum running speed • no effect for peak or minimum power output
Balsom et al. 1993	16 M	25 X 6 = 150	10 X 6 s 130 rpm (~ 820 W) 10 X 6 s 140 rpm. (~ 880 W) cycling	• ↓ fatigue • ↑ BM 1.1 kg (1.3%)
Balsom et al. 1995	7 M	20 g / day, 6 days	5 X 6 s cycling (30 s recovery interval) 10 s sprint 40 s after the series of sprints CMJ, SJ	• ↑ BM 1.1±0.5 kg • ↑ TCr • ↑ PCr after the series of sprints • ↑ in power output maintenance in 10 s sprint • no improvement in CMJ and SJ
Bogdanis et al.1995b	16 M	75 mg/kg BM X 4 times / day X 5 days	VO_{2max} test 16 min submaximal running- increasing intensity (60- 90% $VO_{2\ max}$) 6 X 10 s running sprints (30 s recovery interval)	• no improvement in submaximal and VO_{2max} test • ↑ Performance in repeated sprints • ↑ BM 0.9 kg
Bosco et al. 1997	14 M sprinters and jumpers	20 X 5 = 100 g	45 s repeated jumps (Bosco test) running (20 km/h grade 5%) on treadmill	• ↑ 7% of work in 15 first seconds and 12% between 15–30 s (Bosco test). • ↑ Time to exhaustion (13.2 %)
Casey et al. 1996	9 M	20 X 5 = 100	2 X 30 s isokinetic cycling	• ↑ peak power and total work in 2nd sprint • ↑ PCr in type I and II muscle fibers. ↑ TCr in muscle per 23 mmol/kg wet weight)
Cooke et al. 1995	12 M, untrained	5 g X 4 = 20 g / day, 5 days	2 X 15 s (20 min recovery interval)	• no effect of Cr on power output and total work
Cornish et al. 2006	14 M, ice hockey players	0.3 g / kg BM X 3, 5 days	10 s sprints on skating treadmill (30 s recovery interval) X times until exhaustion (~ 4-6)	• no effect of Cr on time to exhaustion and blood lactate • no effect of Cr on isokinetic torque and power • no effect of Cr in BM
Cox et al. 2002	14 F, soccer players		5 X 11 min testing blocks including: 11 X 20 m running sprints agility tasks: 4.5 m square circuit 1 precision ball-kicking drill	• ↑ in BM from (61.7±8.9 to 62.5±8.9) • ↓ in time for some sprints and agility runs in Cr group
Delecluse et al. 2003	9 M, highly trained sprinters	0.35 g·kg⁻¹·day⁻¹, 7 days	40 m running sprint 6 X 40 m (30 and 120 s recovery interval)	• no effect of Cr on maximal sprint performance • no effect of Cr on fatigue at the end of repeated sprints
Deutekom et al. 2000	23 M, rowers	5 g X 4 = 20 g / day 6 days	Isokinetic contractions 2 X 30 s (4 min active recovery)	• no effect of Cr on fatigue during isokinetic contractions • no effect of Cr on power output during cycling bouts

Earnest et al. 1995	8 M, resistance training	20 X 14 = 280	• Wingate (X 3) • 1 Repetition Maximum (1-RM) • Repetitions in 70% of 1-RM	• ↑ of total work in all Wingate tests • ↑ 6% in 1-RM • ↑ 35% in 70% of 1-RM
Febbraio et al. 1995	6 M	20 X 5 = 100	4 X 60 s cycling 1 X 115 – 125% VO_{2max}	• no significant benefit of Cr
Finn et al. 2001	16 M, triathletes	5 g X 4 = 20 g / day 5 days	4 X 20 s cycling sprints (20 s recovery interval)	• no effect of Cr on mean and peak power • no effect of Cr on fatigue index
Glaister et al. 2006	42 M	5 g X 4 = 20 g / day 5 days	15 X 30 m (repeated every 35 s) indoor running sprints	• no effect of Cr in fastest time, mean time, fatigue • no effect of Cr in Lactate concentration • ↑ in BM (0.7kg) ↓ in body fat (0.4%) in Cr group
Greenhaff et al. 1993 b	12 M / F	20 X 5 = 100	30 maximal isokinetic contractions X 5 sets (1 min recovery interval between the test)	• ↑ in maximal torque in all sets between 1-20 contraction. • ↓ plasma ammonia (NH3)
Grindstaff et al. 1997	18 M / F, young swimmers	21 X 9 = 189	• 3 X 20 s (maximal speed) • 3 X 100 m • 3 X 50 m	• no significant improvement in Cr group • no significant difference in BM
Havenetidis et al. 2006	15 M	Not mentioned	3 X WAnT (30 s / 6 min recovery interval)	• ↑ in mean and peak power output in Cr group
Hoffman et al. 2005	40 M	6 g / day, 6 days	3 X 15 s sprints (1 min recovery interval)	• no effect of Cr in BM • no effect of Cr in power output • ↓ of fatigue between multiple sprints in Cr group
Izquierdo et al. 2002	19 M, handball players	5 X 4 = 20g / day, 5 days	5 X 15 m running sprints (60 s recovery interval)	• no effect in running time of 15 m multiple sprints • ↓ in time for the first 5 m of each sprint
Jones et al. 1999	16 M, ice-hockey players	5 X 4 = 20g / day, 5 days maintenance 5 g X 10 weeks	5 X 15 s cycling sprints (15 s recovery interval) 6 X 80 m skating sprints initiated every 30 s) split time at 47 m	• ↑ in average mean and peak power after Cr loading and after 10 weeks • ↓ in average time for 47 m repeated sprints after Cr loading and 10 weeks
Kamber et al. 1999	10 M, physical fitness students	20 X 5 = 100	10 X 6 s cycling sprints (30 s recovery interval)	• higher speed in last 2 s in sprints 4-10 • ↑ in Cr κατά 9.6 mmol/l (18%) • ↑ in BM 1.4 Kg • no change in CK, Hematocrit, LDL, AST, ALT
Kinugasa et al. 2003	12 M	5 g X 4 = 20 g / day, 5 days	10 X 6 s cycling sprints (30s recovery interval) MRI before and after exercise for substrate use determination	• ↑ in BM (from 62.7±6.8 to 63.7±6.8 kg) • no effect on peak and mean power output • no effect on blood lactate

Kreider et al. 1998	25 M, Soccer players	1.75 X 28 = 441	• 12 X 6 s sprint (30 s recovery interval) • 1-RM bench press	• ↑ in total work in first 5 sprints • ↑ in total work in resistance training • ↑ BM 2.42 kg (2.5%) in Cr group and 0.85 kg in Pl • ↑ in CK, LDH, AST, ALT • ↑ 13% in HDL
Kurosawa et al. 2003	12 M	5 g X 6 = 30 g / day, 14 days	10 s dynamic handgrip exercise (40% of MVC)	• ↑ in mean power output (15.1±3.8%) • ↑ in ATP synthesis rate from PCr • no effect of Cr on ATP cost of contraction
Leenders et al. 1999	32 M / F swimmers	20 X 6 = 120 10 X 8 = 80	• 6 X 50 m (30s recovery interval) • 10 X 25 yd (1min recovery interval)	• improvement in speed (from 1.63 to 1.67 m/s in M. No change in F) • no significant change in performance (10 X 25 yd)
McKenna et al. 1999	14 M and F, physical education students	5 g X 6 = 30 g / day, 5 days	5 X 10s cycling sprints [multiple recovery: 3min (after 1st), 50s (after 2nd), 20s (after 3rd and 4th)]	• ↑ in TCr • no increase in PCr • no effect of Cr on peak power output and total work • no effect on fatigue index
Mujika et al. 1996	20 M / F, swimmers	20 X 5 = 100	25, 50, 100 m	• no improvement in swimming time • ↑ in BM 0.7 kg (1%) • ↓ in plasma ammonia (NH3)
Mujika et al. 2000	17 M, soccer players	5 g X 4 days, 6 days	6 X 15 m running sprints (30 s recovery interval) intermittent endurance test (40 X 15 s with 10 s rest) CMJ	• ↓ in time for 5 m and 15 m runs • no effect on CMJ • no effect on endurance test
Okudan et al. 2005	23 M	5 g X 4 = 20 g / day, 6 days	5 X 30 s WAnT (2 min recovery interval)	• ↑ in mean power in 3rd and 4th WAnT • ↑ 7.6% power output from the 5 WAnT • ↑ in fatigue index in Pl group
Pluim et al. 2006	36 M, tennis plyers	6 days Cr loading 4 weeks maintenance	Tennis specific indices Intermittent running speed (20m)	• no effect on tennis skills • no effect on repetitive sprint power (5, 10, 20m)
Rockwell et al. 2001	16 M	5 X 4 = 20 g / day, 4 days	10 X 6 s cycling sprints (30 s recovery interval)	• ↑ muscle Cr during energy restriction • no effect on BM • tendency for higher total sprint work
Romer et al. 2001	9 M, squash players	4 X 0.075 g·kg⁻¹BM, 5 days	10 sets X 2 repetitions (simulated positional play/ 30 s recovery interval)	• 3.2±0.8% higher improvement of mean set sprint time than placebo group • ↓ in time for sets 2 to 10
Rossiter et al. 1996	38 M / F, rowers	0.25 g/kg BM X 5	1000 m rowing ergometer	• 2.3 s improvement in performance
Skare et al. 2001	18 M, sprinters	5 g X 4 = 20 g / day, 5 days	100 m running, split at 60 m 6 X 60 m sprints, (start every 50 s)	• ↑ in BM 0.6±0.1 Kg • ↓ in time for last 40 m of 100 m • ↓ in total time foe multiple sprints

Snow et al. 1998	8 M	30 X 5 = 150	20 s cycling sprint	• no improvement in performance • no change in PCr • ↑ in BM 1L (1.3%)
Terrillion et al. 1997	12 M, runners	20 X 5 = 100 g / day	700 m running	• no effect of Cr • no significant change in BM
Thompson et al. 1996	10 F, swimmers	2 X 42= 84	100 m swimming 400 m swimming	• no effect of Cr in 100 m and 400 m
Van Schuylenbergh et al. 2003	14 M, cyclists	2 X 3.5 = 7 g / day, 7 days	Endurance cycling test: 1-hour time trial 5 X 10 s sprints (2 min recovery interval)	• no effect of Cr in endurance test • no effect of Cr in multiple sprint test
Ziegenfuss et al. 2002	10 M and 10 F	0.35 g / Kg fat-free mass, 3 days	6 X 10 s cycling sprints (60 s recovery interval)	• ↑ in thigh volume in 5 of 6 Cr participants • ↑ in BM 0.9±0.1 Kg • ↑ in total work in sprint 1 • ↑ in peak power in sprints 2-6

BM = Body mass, WAnT= Wingate Anaerobic Test, M= Males, F=Females, Cr = Creatine, Pl = Placebo group.