AMERICAN COLLEGE of SPORTS MEDICINE$_{SM}$
ROUNDTABLE

The physiological and health effects of oral creatine supplementation

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ABSTRACT

The American College of Sports Medicine Roundtable on the physiological and health effects of oral creatine supplementation. *Med. Sci. Sports Exerc.,* Vol. 32, No. 3, pp. 706–717, 2000. Creatine (Cr) supplementation has become a common practice among professional, elite, collegiate, amateur, and recreational athletes with the expectation of enhancing exercise performance. Research indicates that Cr supplementation can increase muscle phosphocreatine (PCr) content, but not in all individuals. A high dose of 20 $g \cdot d^{-1}$ that is common to many research studies is not necessary, as 3 $g \cdot d^{-1}$ will achieve the same increase in PCr given time. Coincident ingestion of carbohydrate with Cr may increase muscle uptake; however, the procedure requires a large amount of carbohydrate. Exercise performance involving short periods of extremely powerful activity can be enhanced, especially during repeated bouts of activity. This is in keeping with the theoretical importance of an elevated PCr content in skeletal muscle. Cr supplementation does not increase maximal isometric strength, the rate of maximal force production, nor aerobic exercise performance. Most of the evidence has been obtained from healthy young adult male subjects with mixed athletic ability and training status. Less research information is available related to the alterations due to age and gender. Cr supplementation leads to weight gain within the first few days, likely due to water retention related to Cr uptake in the muscle. Cr supplementation is associated with an enhanced accrual of strength in strength-training programs, a response not independent from the initial weight gain, but may be related to a greater volume and intensity of training that can be achieved. There is no definitive evidence that Cr supplementation causes gastrointestinal, renal, and/or muscle cramping complications. The potential acute effects of high-dose Cr supplementation on body fluid balance has not been fully investigated, and ingestion of Cr before or during exercise is not recommended. There is evidence that medical use of Cr supplementation is warranted in certain patients (e.g., neuromuscular disease); future research may establish its potential usefulness in other medical applications. Although Cr supplementation exhibits small but significant physiological and performance changes, the increases in performance are realized during very specific exercise conditions. This suggests that the apparent high expectations for performance enhancement, evident by the extensive use of Cr supplementation, are inordinate. **Key Words:** PHOSPHOCREATINE, EXERCISE PERFORMANCE, STRENGTH DEVELOPMENT, TRAINING

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INTRODUCTION

Renewed interest in the effects of phosphocreatine (PCr) has been kindled by recent research demonstrating that creatine (Cr) supplementation can increase skeletal muscle PCr content in some individuals and enhance exercise performance in some activities. Superb achievements by some elite athletes have been perceived as related to Cr supplementation. This along with considerable media attention has led to a common perception that Cr supplementation is beneficial and *de facto* "essential" to sport achievement. There is a wide-spread use of Cr supplementation by professional athletes, elite sports competitors, collegiate athletes, amateur and recreational athletes, and hopeful teenage athletes, all apparently without great understanding of the applicable research. It can be estimated that Cr consumption this past year exceeded more than 2.5 million kg. Restated, this is a staggering 2.5 thousand metric tons. This defines an enormous expectation for potential benefit. Further, a belief common in athletic competition espouses the practice that if a little is good, then more is better. This misconception can, in general, lead to a behavior of excess and to an exposure of potential health risks.

Although Cr supplementation is perceived as relatively "safe," there has been little critical evaluation of its health implications. Similarly, there appears to be little appreciation of research evaluating Cr supplementation, the nature of its potential impact on exercise performance, and its application to specific sport activities. This raises the potential that the expectations for Cr supplementation are excessive and potentially misleading. For these reasons, the American College of Sports Medicine commissioned a Roundtable panel of scientific experts to provide a synthesis of the topic. Questions related to the biochemical, physiological, exercise performance, and potential health effects and clinical application of Cr supplementation were addressed.

What Is Creatine, How Is It Metabolized in the Body, and What Is the Impact of Cr Supplementation?

Creatine is a nonessential dietary element found in high abundance in meat and fish. It is synthesized within the body, primarily in the liver, from two amino acids by a two-step reaction. In the first step, guanidinoacetate is formed from arginine and glycine in a reaction catalyzed by arginine:glycine

amidinotransferase. In the second step, a methyl group of S-adenosylmethionine is transferred to guanidinoacetate and Cr is formed (9,115). Muscle does not synthesize Cr but is dependent on Cr uptake from the circulation by a sodium dependent transporter in the muscle membrane. Once in the myocyte Cr becomes phosphorylated by the activity of Cr kinase, the actual distribution between Cr and PCr is determined by the energy state of the cell. Important to the discussion of this report, Cr ingestion has been shown to reduce endogenous Cr synthesis in animals, likely by the down-regulation of the rate-limiting enzyme amidinotransferase (115,116). The results of tracer (41) and Cr balance (46,115) studies indicate that Cr ingestion also reduces endogenous Cr synthesis in man. Thus, it can be expected that Cr supplementation, especially large quantities, serves to markedly reduce normal Cr synthesis in the body. Whether this adversely affects metabolic regulation within the liver is unclear; however, it may be presumed that after a brief period after the cessation of Cr supplementation, Cr synthesis within the body would revert to its preexisting rate. The long half-life of Cr in muscle likely provides for a buffer that would allow for the recovery of any potential down-regulation in either synthesis or transport.

Creatinine. The sole end product of Cr metabolism is creatinine, formed by the nonenzymatic conversion from PCr and Cr (41,115). This occurs at a rate of approximately 2% of the body's total Cr pool per day (41,76). Creatinine is excreted by the kidneys at a rate of approximately 2 $g \cdot d^{-1}$ for an average adult. Because skeletal muscle contains most of the body's PCr and Cr pool, the urinary excretion of creatinine will vary as a function of muscle mass, being on the average less in female than male subjects. Vegetarians have marginally lower urinary creatinine excretion rates than subjects with normal diets, suggesting that the Cr biosynthesis rates and the muscle Cr contents are also marginally lower than in subjects ingesting Cr containing diets (21).

Short-term Cr supplementation. A careful study of Cr-creatinine balance performed nearly 75 years ago (15) employing ingestion of 10–20 g $Cr \cdot d^{-1}$ demonstrated that intestinal absorption of Cr is close to 100%, that urinary creatinine excretion increases slowly in time, that most of the ingested Cr is retained by the body in the first few days, and that most of the ingested Cr (90%) is excreted as Cr in the urine with continued daily supplementation. Thus, although most of the oral Cr consumed is absorbed and enters the circulation, not all is retained in the body. When the capacity of the muscle to extract Cr from the blood appears to be exceeded, which occurs in the first several days, the excess Cr is simply excreted into the urine. As a result, continued ingestion of large doses of Cr simply establishes Cr-enriched urine. In more recent work, Hultman and coworkers (39,45) have confirmed the extensive retention of Cr after the initiation of Cr ingestion and extended our understanding to show that the majority of retained Cr was in the muscle. Coincident with the retention of Cr, there is a substantial reduction in urine production on the first 3 d of the loading period (45). This retention of water is thought to be related to an osmotic load caused by Cr retention (121) and to account for the rapid-onset weight gains experienced by individuals ingesting Cr. Many studies have reported increases in body mass of 1–3 kg after short-term (5–7 d) Cr supplementation (54,72,112–114,117). One study that examined Cr supplementation in women found smaller increase in body mass compared with results of other studies in men (108), which could be due to their smaller muscle mass. Similarly, healthy older men supplemented with Cr (20 $g \cdot d^{-1}$ for 5–10 d) exhibited either no (84) or a small (0.5 kg) increase in body mass (83,84). Retention of Cr in the skeletal muscle would result in muscle enlargement due to water absorption; however, this short-term skeletal muscle enlargement is not typical of that induced by "strength" training, which results in the accrual of contractile and structural protein that is associated with "true" muscle hypertrophy.

What Are the Roles of the Phosphocreatine/Creatine System in Muscle?

PCr serves as a readily available source of ATP in skeletal muscle and other tissues. Based on numerous studies conducted over the last several decades (reviewed in 16,38,61,62), there are four general aspects to its function in muscle. First, the rapid rephosphorylation of ADP from PCr via the Cr kinase reaction buffers changes in ATP during transitions between rest and exercise, and contributes a substantial fraction of ATP synthesis during short-duration, high-intensity exercise. Second, because of the intracellular localization of Cr kinase isozymes at both sites of ATP synthesis (mitochondria) and use (myofibrils, SR membrane, etc.), PCr and Cr enhance the capacity for high-energy phosphate diffusion between these sites within the cell. Third, because net PCr hydrolysis consumes hydrogen ions, PCr hydrolysis may contribute to buffering of intracellular acidosis during exercise. Fourth, the products of PCr hydrolysis (Cr and inorganic phosphate) play a role in activation of glycogenolysis and other catabolic pathways.

Exercise type. The relative importance of PCr during exercise is dependent on the nature of the exercise. For most exercise situations, the demand for ATP is predominantly provided through oxidative phosphorylation in the mitochondria. However, under some conditions aerobic energy production cannot meet the demand for ATP. In these cases, anaerobic energy production from PCr hydrolysis and glycogenolysis/glycolysis is required to assist in the provision of ATP (5,96). Such cases include the transition from rest to exercise, the transition from one power output to a higher power output, at power outputs above 90–100% maximal oxygen consumption ($\dot{V}O_{2max}$), and in situations where the availability of oxygen has been reduced (e.g., altitude exposure).

Intense exercise. The relative importance of PCr hydrolysis as an energy source during contractions varies with the intensity, duration, and frequency of the exercise (44). For example, during a 6-s sprint at a power output representing ~250% $\dot{V}O_{2max}$, PCr hydrolysis and glycolysis

each contribute ~50% of the total ATP requirement with very little contribution from oxidative phosphorylation (30). On the other hand, during a 30-s sprint averaging ~200% $\dot{V}O_{2max}$, glycolysis contributes ~55% of the total ATP requirement, PCr hydrolysis 25%, and oxidative phosphorylation 20% (5,82,96). This relative shift away from PCr as a source of ATP is a consequence of the limited supply of PCr in muscle (~70–90 mmol·kg^{-1} dry wt) relative to the ATP turnover rates which occur in muscle during contraction (up to 10–15 mmol·kg^{-1}·s^{-1}). Thus, the relative importance of PCr hydrolysis to ATP synthesis during a bout of intense exercise bout falls off dramatically as the exercise duration is increased well beyond a few seconds.

What Is the Potential for an Increased PCr/Cr System to Improve Energy Supply during Exercise?

Creatine supplementation is reported to increase muscle PCr content by approximately 20%, or from ~70–90 to ~85–105 mmol·kg^{-1} dry weight (28,39,45). In view of the above, by what mechanism and under what circumstances would Cr supplementation be expected to impact exercise performance? It is unlikely that Cr supplementation would improve performance during aerobic exercise in normal subjects, because the normal content of PCr is sufficient to maintain ATP supply during the transition period (3,110). Furthermore, although PCr and Cr are important for steady-state transport of high-energy phosphates from the site of production (mitochondrion) to the site of use (myofibrils) within the cell, the normal content of Cr in muscle is more than adequate to fulfill this role (38,43,62). Thus, our focus should be on exercise conditions that are nonsteady state and/or where the aerobic energy supply is inadequate.

Intense exercise. At higher exercise intensities, the effect of Cr supplementation would depend on the magnitude of the PCr increase achieved relative to the ATP turnover rate, and relative to the other available sources of ATP. For example, if a 10–20% increase in PCr was achieved by Cr supplementation, this might be expected to improve performance during a 30-s sprint (when PCr hydrolysis normally accounts for about 25% of the total ATP use), due to the 2.5–5% increase in energy supply. Such a marginal performance increase could be difficult to detect given the experimental variance of human performance measurements. On the other hand, greater gains in performance might arise under conditions in which PCr contributes a larger fraction of the total ATP supply. For example, during repeated exercise paradigms (30-s sprints, separated by 4-min rest periods), it becomes increasingly difficult to restimulate the glycogenolytic/glycolytic pathway for ATP provision (96). Provided that the rest periods are sufficiently long to allow for rephosphorylation of a large fraction of PCr by oxidative phosphorylation, any increase in the total Cr pool would have a greater impact on performance during the subsequent repeated bouts. For example, if by the third sprint in this scenario, the fraction of ATP supplied by PCr increased to 50%, then a 10–20% increase in PCr from Cr supplementation could translate into a 5–10% increase in energy supply, and thereby improved performance, compared with the control condition. Similarly, even if there were not sufficient time for full PCr recovery between subsequent exercise bouts, an increase in [PCr] with Cr supplementation would be expected to increase energy supply above the control condition. Although the precise benefit is difficult to calculate, the extent is limited by the realized increase in [PCr] present at the time of initiating the subsequent intense exercise bout. Thus, if Cr supplementation is to impart a potential benefit in energy provision, it would be during short-term, very high-intensity exercise, especially when performed in repeated succession.

Cr supplementation considerations. Despite the potential for gain in "performance" from Cr supplementation, it should be noted that the changes in muscle total Cr and PCr caused by Cr supplementation do not mimic any adaptive changes that occur in response to exercise training programs. Neither aerobic, high-intensity resistance, nor sprint training is accompanied by significant changes in PCr, total Cr content, or Cr kinase activity (65,75). Cr supplementation cannot replace the necessity and value of training for conditioning and/or sport preparation. Further aspects of Cr supplementation should be kept in mind. First, although the performance of muscle is clearly better in the presence of the PCr/Cr system than in its absence (56,62,87), PCr is not "essential" for muscle contraction. ATP is the essential high-energy compound involved in muscle contraction. Second, based on the available evidence, Cr supplementation does not increase the potential energy available from PCr hydrolysis. On the contrary, available studies suggest that the PCr/Cr ratio in muscle decreases after supplementation (28,39,45), which would naively suggest a smaller free energy potential. Because this is contrary to expectations, these measurements from muscle supplemented with Cr are viewed with some uncertainty. Third, although an increase in total Cr content in muscle could result in a greater *oxygen deficit* (34,61), there is no evidence that Cr supplementation increases the *aerobic power* of muscle. Thus, the exercise context for potential impact of Cr supplementation seems well defined. Finally, there is no evidence that Cr directly stimulates protein synthesis or alters myosin expression in normal differentiated muscle cells (29,119). Thus, there is no presently identified anabolic effect of Cr supplementation.

Muscle fiber type. The above discussion has not addressed the issue of fiber type differences in skeletal muscle. Measurements on human single skeletal muscle fibers or pools of fibers of a specific fiber type have revealed that the resting PCr content is 5–15% higher in Type II vs Type I fibers (36,95). In addition, the rate of PCr degradation is faster in Type II vs Type I fibers during sprint exercise lasting 10–30 s (36). On the other hand, the Type I fibers initially resynthesize PCr at a slightly faster rate than Type II fibers during recovery from sprint exercise (95). After Cr

supplementation, both fibers increase total Cr and PCr contents, with a trend toward a larger increase in Type II fibers (13). Thus, the relationship between the fiber types regarding PCr use during exercise and resynthesis after exercise is unchanged.

Does Cr Supplementation Increase Skeletal Muscle Cr and PCr Concentrations?

The answer to this question is usually yes, but the extent can be quite variable and there are a number of caveats that are important to consider. Based on initial work (34,39,45), a commonly used dose to evaluate the effects of Cr supplementation has been approximately 20 g of Cr ingested per day for 4–6 d; this represents a dose of ~0.3 g Cr·kg^{-1} body weight·d^{-1} for an average adult. Generally, Cr has been ingested in 5-g doses, four to five times per day. The ingestion of 5 g of Cr in solution will raise the plasma Cr concentration approximately 15–20 fold, from ~40 μmol·L^{-1} to 600–800 μmol·L^{-1} within 1 h; plasma levels then decrease to close to basal over the subsequent 5 h (33,39). Repeating this procedure on 4 evenly spaced occasions each day for 5 d can increase the muscle total Cr store by a rather variable extent, from zero (0%) to up to 40% depending on the individual (34,39). Thus, there are "nonresponders." The reasons for the variability in response is unclear; however, the extent of Cr uptake is inversely related to the individual's initial muscle total Cr content. The lower the initial muscle Cr concentration, the greater is the increase with Cr supplementation (39). Conversely, the higher the initial muscle Cr concentration, the more difficult it is for the individual to realize an increase in total muscle Cr. This may be related to a yet unrecognized process in the muscle that serves to control the upper limit of the total Cr content in the cell. For example, there is recent evidence that the muscle Cr transport protein is down-regulated in animal skeletal muscle after long-term high-dose Cr supplementation (38). If the Cr transporter protein is likewise decreased in humans, there could be a tempered muscle uptake of Cr from the plasma. The practical effect seems to be that there is an upper limit to the muscle total Cr content. This probably explains why some studies did not find, on the average, any significant increase in total Cr content. However, most studies report an average response of an approximate 15–20% increase for the entire group (e.g., 13,39,45,86). This increase in muscle total Cr is comprised of increases in both free Cr and PCr, with the magnitude of increase in free Cr being the greatest. Thus, some studies report a significant increase in total Cr with supplementation, but without a significant increase of PCr being measured. The majority of muscle Cr accumulation occurs in the initial 2 d and, as total Cr accumulation is maximized, there is Cr spillover in the urine. Therefore, extended days of ingesting ~20 g Cr·d^{-1} is unwarranted.

Cr, exercise, and carbohydrate loading. Submaximal exercise performed before Cr ingestion can augment muscle Cr accumulation by approximately 10%, but again the variation in response is marked among individuals (39). The enhanced Cr accumulation is not a generalized response but is specific to the exercised muscle, because the nonexercised contralateral muscle of individuals who supplemented with both Cr plus carbohydrates (CHO) did not increase to the same extent as the active muscle (86). Muscle Cr accumulation can be substantially augmented by ingesting Cr in combination with large quantities of simple CHO (32). This increases the magnitude of both muscle PCr and Cr accumulation and reduces the variation in responses among individuals. It also outweighs any stimulatory effect that exercise may have on muscle Cr accumulation (32,33). Muscle Cr accumulation is thought to be augmented as a result of insulin stimulating muscle sodium pump activity and thereby the sodium-dependent Cr transport. Recent evidence has demonstrated that ingestion of approximately 100 g of simple CHO with each 5 g Cr dose is required to achieve an insulin-mediated stimulation of muscle Cr transport (97), the process likely contributing to the enriched Cr accumulation. The authors demonstrated that this large quantity of CHO is necessary to raise the serum insulin concentration to the high levels (>100 mU·L^{-1}) required to augment muscle Cr transport. In practical terms, the repeated ingestion of such a high CHO load with Cr supplementation (e.g., as commonly done 4 times·d^{-1}) would be difficult for athletes to achieve. It should also be noted that the magnitude of muscle Cr accumulation is reduced when Cr + CHO are ingested after prolonged exercise, likely due to an exercise-induced blunting of insulin release (85).

Cr dose. Whereas most studies have employed a "loading" dose of ~20 g Cr·d^{-1} for 4–6 d, likely because the initial studies (2,35,39) employed this dose, ingesting Cr at a much lower dose of 3 g·d^{-1} will increase muscle total Cr to the same values observed with 5 d of 20 g·d^{-1}; however, it takes longer (~30 d) (45). Thus, the high "loading" dose of Cr of 20 g·d^{-1} (i.e., ~0.3 g Cr·kg^{-1}·d^{-1}) is unnecessary to realize an increase in muscle Cr content. Once muscle Cr is elevated, ingesting only 2 g Cr·d^{-1}, as a single daily dose, was sufficient to maintain Cr stores (45). Ingesting 2 g Cr·d^{-1} maintains muscle Cr delivery at slightly above the rate of muscle Cr degradation to creatinine. Urinary creatinine output increases by about 20%, which parallels the increase in muscle total Cr content (45). When Cr ingestion was stopped after the initial Cr-loading phase that was used (e.g., 5 d at 20 g Cr·d^{-1}), muscle Cr stores decline gradually to basal levels, without an undershoot, after approximately 4 wk (28,45).

Does Cr Supplementation Enhance Exercise Performance?

Short-term Cr supplementation (e.g., 5–7 d of ~20 g·d^{-1}) can lead to an improvement in performance. Most (2,4,8,10,13,20,24,25,31,35,40,48,60,74,79,88,94,112–114) but not all (6,11,18,19,28,64,67,85,93,103) of the studies indicate that Cr supplementation significantly enhances the ability to produce higher muscular force and/or power

output during short bouts of maximal exercise in healthy young adults. Subjects in these studies have been of mixed athletic ability and training status, from relatively untrained novices to competitive college level athletes. At present, exercise performances that are improved include: various protocols of short-term, all-out cycling (2,4,8,13,20,25,48,79,94,110), sprinting (10,24,40), repeated jumping (10,114), swimming (37,74), kayaking/rowing (60,88), and resistance-exercise performance (25,31,35,114). Interestingly, the greatest improvements in performance seem to be found during a series of repetitive high-power output exercise bouts (2,4,8,10,20,35,79,114). Exercise performance during the latter bouts of a series (e.g., third, fourth, fifth) can be increased by 5–20% over that measured for the placebo group. These experimental protocols typically employed exceptionally high-power output efforts (e.g., maximal cycling and/or power jumping that can be maintained for only a short period, usually seconds) separated by fairly brief periods of rest (e.g., 20–60 s). As discussed above, these are the exercise conditions where the transitional energy contribution from PCr is likely most significant; further, the short-term rest periods between bouts are apparently sufficient to permit an enhanced recovery of the muscle PCr concentration in those individuals with a greater total Cr concentration. Greenhaff and coworkers (34) found a greater PCr resynthesis after PCr depletion caused by maximal ischemic exercise in individuals with a supplemented total Cr content; however, this response is expected to be less with less intense exercise where there is only partial PCr depletion and/or in individuals with initially high total Cr stores in the muscle (109). Although not yet established experimentally, this is an example where an enhancement in exercise performance matches the expectations identified from our knowledge of fundamental energetics of PCr in muscle.

Study reproducibility. It is unclear why there has not been a uniform response across studies; however, a number of factors in the experiments may be contributors, including: a placebo effect evident in the experiment, the relatively small magnitude of the treatment effect, the heterogeneous group of performance tasks used in these studies, a relatively large test-retest reliability error in the measurement of the performance task, and the possibility that the magnitude of the response appears to be a function of the magnitude of muscle Cr increase (13,34,36). Although the former sources of error lead to spurious and/or false negative outcomes, the latter issue implies that some of the subjects that are "non-responders" for increased muscle Cr would be also expected to exhibit no increase in performance; this would add variability and undermine the potential of demonstrating a response in those subjects who "responded." Regardless of these uncertainties, it is likely that Cr supplementation improves exercise performance in events that require explosive, high-energy output activities especially of a repeated nature.

Muscle force. Creatine supplementation has been found to shorten muscle relaxation time, particularly in individuals with slow initial muscle relaxation rates (106). This effect is thought to be due to a facilitation of sarcoplasmic reticulum Ca^{2+} ATPase activity evident in Cr-supplemented muscles (22,81). Presently, it is not known whether this response has any relationship to the improved exercise performance observed during repetitive short-term high-power exercise bouts. Interestingly, several studies have reported an improvement in 1 RM dynamic strength, which is determined by 3–6 progressive contraction efforts to establish maximum (54). This has led to the mistaken belief all maximal strength measures are enhanced by Cr supplementation. On the contrary, it is important to recognize that Cr supplementation does not increase maximal isometric muscle strength (107), neither does it alter the rate of maximal force production (106).

Aerobic exercise. Creatine supplementation does not appear to enhance aerobic-oriented activities (3,110). This is in keeping with the expected near trivial contribution of PCr to the net energy expenditure of aerobic exercise. Interestingly, Cr supplementation has been shown to have a positive effect (~30%) on the power production during short sprints that were required within and at the end of an endurance exercise-training session (27,110). Whether such a change in the intensity of the endurance-training sessions might affect subsequent sport performance in competitive endurance events has not been directly studied.

Age and gender. Although there is a paucity of information about the response of women to Cr supplementation, it appears that gender is not a determining issue (108). The majority of the performance data have been generated with men as subjects. In fact, a fairly narrow age group of men, between 18–35 yr, has been used. One exception investigated the effect of Cr supplementation on intermittent sprint performance in swimming in young individuals under the age of 18 yr (37). In keeping with the observations of other studies using young adult subjects, a marginal improvement in performance was reported. On the other hand, only four studies employing short-term Cr supplementation have involved older individuals. In the first, four subjects (mean age of 58 yr) exhibited an increased muscle PCr concentration and an improved time to exhaustion during knee extension exercise (37 contractions·min^{-1}) after 5 d of 0.3 g·kg^{-1}·d^{-1} Cr supplementation (92). Rawson and Clarkson (83) demonstrated that healthy older men (60–78 yr) supplemented with Cr (20 g·d^{-1}) for 5 d showed a marginal improvement in exercise performance (3 sets of 30 isokinetic contractions) and no change in maximal isometric strength. Rawson et al. (84) also found that 30 d of Cr supplementation (20 g·d^{-1} for 5 d; then, 4 g·d^{-1} for 20 d) in 60- to 82-yr-old men had minimal effect on performance. Furthermore, in a study that involved 8 wk of Cr ingestion (20 g·d^{-1} for 5 d, 3 g·d^{-1} for 47 d), Bermon et al. (7) reported no changes in lower limb volume, body mass, or percent fat in 32 healthy elderly subjects that took part in an 8-wk resistance-training program. Creatine supplementation did not induce any additional strength gains or resistance to fatigue compared to the group with resistance training alone.

Thus, the weight of the data to date suggests that older subjects do not respond to Cr supplementation to the extent shown for young subjects. The basis for this is presently unknown.

Chronic Cr supplementation. Few data exist on the long-term benefits and risks of Cr supplementation in men and women. A number of studies indicate that Cr supplementation in conjunction with heavy-resistance exercise training (e.g., 4–12 wk in duration) enhances the normal physiological adaptations to the weight-training program (51,55,66,73,108,112). Typical training adaptations, including increases in body mass, fat-free mass, maximal strength and power, lifting volume, and muscle fiber hypertrophy (73,108,112), are all significantly enhanced concurrent with Cr supplementation. These studies have been conducted without any discernible adverse effects of the Cr supplementation. In a recent study, Pearson et al. (72), showed that Cr supplementation of 5 $g \cdot d^{-1}$ over 10 wk of resistance training results in significant increases in strength and body mass over that realized by the placebo group. This study indicates that similar training gains can be achieved on lower doses of Cr supplementation. Interestingly, enhancement of these training adaptations with Cr supplementation were observed even when the training stimulus was fixed (108). Thus, the outcome could not be simply explained by the ability of the subjects to perform a greater volume of lifting, which could impart a potentially greater adaptive stimulus. On the other hand, the achievement of a greater volume of lifting in the training program, apparent with Cr supplementation, should further enhance the training stimulus. The reasons for the outcome of these studies is intriguing. On one hand, there is an apparent specific effect of Cr supplementation that operates to enhance muscle performance and the adaptive response to overload training. For example, if the increase in water retention that occurs with Cr supplementation were to enlarge muscle volume and this in turn could in some manner alter force/power development, there could be a real enhancement of muscle performance. On the other hand, findings of these studies may be related to a real phenomenon that is coupled with the process of Cr supplementation. For example, the increase in body weight gain is usually readily apparent to individuals beginning Cr supplementation. This could betray the presence of the treatment group and thereby establish an inherent bias. Altered outcome in test evaluation is a commonly observed consequence of subject perception that they are included in the treatment group (104). Further, work is needed to explore which alternatives may be correct and/or discover the basis for the outcome of these interesting studies.

Are All Available Forms of Cr Equal, and Does the Inclusion of Other Nutrients Help?

Commercial Cr supplements are marketed in different forms, primarily Cr monohydrate. Other Cr-containing commercial products contain additional dietary constituents theorized to augment the ergogenic effects of Cr supplementation, including glucose, high-quality protein, vitamins, minerals, ribonucleic acid (RNA), L-glutamine, taurine, β-hydroxy-β-methylbutyrate (HMB), α-ketoglutarate, and herbal extracts. Commercial products are available in a variety of formats, including powder, candy, gum, and liquid.

In general, available research indicates that use of different forms of Cr (73) or various commercial Cr products containing additional dietary constituents (98,99) does not provide any additional response beyond those attributed solely to Cr supplementation. One study indicates that concomitant caffeine intake, as pure caffeine, may negate the Cr supplementation effect on muscle contractile performance (107). However, concomitant use of caffeinated beverages, particularly coffee, does not appear to confound, as studies evaluating the effects of Cr supplementation often used coffee as the delivery vehicle. The concomitant ingestion of large amounts of carbohydrate (~100 g) with each Cr supplement also seems unwarranted because of the high-calorie intake and potential health consequences of high sugar intake over time.

Are There Documented and/or Potential Side Effects of Cr Supplementation?

There are numerous anecdotal reports of Cr supplementation causing gastrointestinal, cardiovascular, and muscular problems. As described below and with notable exception, the evidence is not definitive and/or it is incomplete to indict the practice of Cr supplementation as a health risk; at the same time, our lack of information cannot be taken as assurance that Cr supplementation is free from health risks. Ignorance provides little comfort of untoward effects yet to be discovered.

Nausea/vomiting/diarrhea. There are only anecdotal reports of Cr supplementation being associated with nausea, vomiting, and/or diarrhea (110); however, several blind performance studies that used pure Cr have failed to support this observation (37,55,108,112). It is possible that co-ingestion of other substances may account partially for these reports (e.g., sugars are often co-ingested and excessive amounts may confound gastric emptying and/or absorptive capacity of the gut). The ingestion of Cr during exercise, however, may be problematic; one study did find that 4 of 12 male subjects experienced postexercise "distress" when taking creatine during exercise after a Cr load, whereas no "distress" was reported when the men took placebo (110). Thus, taking high doses of Cr immediately before and/or during exercise is not recommended.

Renal function. Creatine supplementation increases urinary Cr and creatinine excretion (39). Thus, it would be expected that Cr supplementation will increase plasma creatinine concentrations slightly in healthy individuals; there is no *a priori* reason to expect that an increase in the rate of creatinine presentation to the nephron would be otherwise deleterious. Supporting evidence comes from two studies

which show that short-term Cr supplementation does not significantly increase nor alter renal glomerular filtration rate (GFR) (77). Similarly, long-term Cr supplementation (up to 5 yr) did not impair renal function in healthy athletes (78). In long-term Cr supplementation, there can be a modest increase in plasma creatinine concentration that is not within the supra-physiological range. In fact, mild elevations are sometimes observed even in the absence of Cr supplementation due to large muscle masses, and/or exacerbated with high meat intake, of individuals in some strength sports (42,49,59,71).

There is a single case report of a 20-yr-old mam taking Cr (5 g 4 times per day) for 4 wk who presented with clinical and biopsy proven interstitial nephritis that improved with Cr cessation (53). The cause of the nephritis due to Cr supplementation was not established. A 25-yr-old man with focal segmental glomerular sclerosis exhibited an elevation in plasma creatinine and reduction in GFR in response to Cr supplementation (5 g 3 times per day for 1 wk, then 2 $g \cdot d^{-1}$ for 7 wk). These changes reversed after cessation of Cr supplementation for 1 month. Although this is the only report of an association of renal dysfunction and Cr supplementation (80), it serves as notice of the potential confounding nature of Cr supplementation in patients with preexisting renal disease. Thus, for individuals with preexisting renal dysfunction or those at high risk for renal disease (i.e., diabetes, family history of kidney disease), it is recommended that they be monitored medically.

Liver. A single report, demonstrating an elevation in plasma transaminases (AST, ALT) and LDH with Cr supplementation, cannot be taken as definitive of altered hepatic function. The elevated activities of the marker enzymes were most likely due to exercise induced muscle response, as the activity of CK was also higher (55).

Cardiovascular. There have been a few anecdotal reports of hypertension among athletes who Cr supplement; however, in a double-blind study, there was no evidence of an effect of short-term Cr supplementation (20 $g \cdot d^{-1} \times 5$ d) on systolic, diastolic, nor mean blood pressure in young male and female subjects (63). Similarly, in a longer-term study, there was no evidence of any alterations in blood pressure with Cr supplementation (73). Interestingly, Cr supplementation did not alter blood pressure in patients with congestive heart failure (1,31). Further, in one of these studies, pump function of the heart, assessed by ejection fraction determined by echocardiography was not influenced by Cr supplementation (31). Therefore, any potential fluid shifts that may occur with Cr supplementation did not alter cardiac performance. The safety of Cr supplementation in other cardiovascular disorders (e.g., atherosclerotic heart disease) has not yet been determined.

Heat exhaustion. There is no direct evidence that Cr supplementation contributes to the development of dehydration or heat exhaustion. There was much media attention given to three deaths in wrestlers who performed very extreme fluid restriction and other rapid weight loss techniques. A Center for Disease Control review concluded that the rapid weight loss regimen of exercise in the heat and fluid restriction resulted in the hyperthermia/vascular collapse that contributed to their death (14). Thus, Cr supplementation was not implicated in these deaths.

Preliminary evidence indicated, however, that Cr supplementation is not free from its impact on fluid balance in certain sport situations. Combative athletes who were asked to mimic what wrestlers do to "make weight," (i.e., lose 5% of body mass in 5 d) lost less weight while Cr supplementing (20 $g \cdot d^{-1}$ for 5 d) than those individuals on a placebo of glucose loading. Along with this apparent fluid retention on Cr, there was a small decrement in calculated plasma volume. If this preliminary observation is upheld in more precise studies, there are concerns about the possibility of altered fluid balance, and impaired sweating and thermoregulation in athletes acutely loading with Cr in settings where there is the potential for thermal stress (68). Thus, our present recommendation for individuals wishing to control weight and who are subjected to strenuous exercise and/or hot environments is to avoid Cr supplementation. Further, high-dose Cr supplementation (i.e., 20 $g \cdot d^{-1}$) should be avoided during periods of increased thermal stress, such as sports activities performed under high ambient temperature/humidity conditions.

Muscle cramps/strains/damage. There have been a number of reports of cramping, strains and "stiffness" in athletes taking Cr (50,90). In controlled studies, with football players randomized to Cr or placebo during training, there were no increased reports of these events reported in those on Cr (55). In active, young male and female subjects, there is no effect of short-term Cr supplementation (20 $g \cdot d^{-1}$ for 5 d) on resting Cr kinase (CK) activity (63). Football players training while on Cr supplementation (15 $g \cdot d^{-1}$ for 30 d), have shown higher plasma CK activities as compared to placebo; however, their lean mass and possibly, training intensity may have been higher (55). Similarly, in 81 patients with neuromuscular disease, only one subject complained of cramping while supplementing with Cr (10 $g \cdot d^{-1}$ for 5 d to greater than 5 $g \cdot d^{-1}$ for 5 d) (100). However, re-challenge of this patient did not result in any cramping. Further, plasma CK activity does not change as a result of Cr loading in patients with neuromuscular disease ($N = 24$; 5 $g \cdot d^{-1}$ for 6 months). Thus, there is no definitive evidence from controlled studies that implicates Cr supplementation in muscle dysfunction and/or complications in healthy individuals and/or patients with neuromuscular disease. Athletes should consume adequate water and electrolytes as these are likely the most common cause of muscle cramps. Severe or recurrent cramps should be investigated to eliminate clinical entities such as: electrolyte disorders, muscle enzyme deficiency, sickle cell trait, etc. Similarly, an elevated plasma CK activity should be investigated, not simply attributed to Cr supplementation, to identify the cause, i.e., eccentric exercise, cardiac ischemia, metabolic myopathy, inflammatory myopathy, etc.

Pediatric/pregnancy/lactation. There is only a single study looking at the effect of Cr supplementation in the

teenage population; no side effects were reported (37). Nevertheless, the data on potential and real side effects in the pediatric (<18 yr) population is grossly inadequate from which to formulate valid conclusions as to the risk/benefit ratio of Cr supplementation. Thus, Cr supplementation is not advised for the pediatric population (i.e., <18 yr of age). Further cautions about Cr supplementation come from the absence of evidence on the potential for placental transfer of Cr to the fetus. Thus, it is inadvisable for pregnant women to use Cr until appropriate evidence is obtained. Similar cautions are established by the presence of Cr excreted into breast milk; it is not known whether Cr excreted into the breast milk would be increased with Cr supplementation.

Are There Potential Clinical Uses for Cr Supplementation?

There are an increasing number of individuals with a variety of disorders who are using therapeutic exercise (i.e., post-MI, neuromuscular disease, postoperative orthopedic surgery, etc.). Many disease conditions exhibit muscle atrophy and premature muscle fatigue and strategies that may temper these effects could have functional significance to these individuals. Although the list of disorders in which the use of Cr supplementation may be of potential utility is long, we shall only review those conditions where there is some experimental rationale for the use of Cr supplementation. There is some evidence of a beneficial effect in particular patients. Thus, there is the hope that Cr supplementation can influence morbidity, at least in some patients; the outlook is strongest where the clinical problems most carefully match the physiological and biochemical effects of Cr in the cell.

Congestive heart failure. It is known that cardiac CK activity and Cr content are reduced in patients with left ventricular hypertrophy (47). By inference, improving contractile function and/or recovery of Cr concentration might improve cardiac function in patients with congestive heart failure. Although there was no effect of Cr supplementation on the ejection fraction of such patients (31), exercise at a greater intensity could be performed after Cr supplementation (1,31).

Atherosclerotic heart disease. Comparative evidence from animals suggests that Cr supplementation could be useful in ischemic heart disease. For example, PCr introduction into cardiac cell strips increased isometric tension development and partially attenuated the negative effects of hypoxia (105). Creatine supplementation in rats was found to provide myocardial cytoprotection in those exposed to an increased oxidative stress (17). Although there is little relationship to known effects of Cr, Cr supplementation was shown to lower plasma total cholesterol, TG, and VLDL-cholesterol (23). On the other hand, in rats fed Cr for 21 d, there was no enhancement in the recovery of myocardial contractility after ischemia as compared with those treated with placebo (69). To date, there have been no human studies that have evaluated the merits of Cr supplementation in either primary or secondary cardiovascular prevention.

Neuromuscular disease. Decreases in muscle PCr concentrations are found in conditions of inflammatory myopathy (70,100), mitochondrial cytopathy (26,57,100,102), and muscular dystrophy (100,120). Muscle weakness and atrophy are common outcomes in these disorders and contribute to disability and handicap. The provision of Cr to mdx myotubes in culture resulted in higher PCr concentrations, improved survival, and lesser Ca^{2+} accumulation in response to metabolic and mechanical stressors (38). In a randomized, double-blind, cross-over study, it was found that Cr supplementation (dose range between: 10 $g \cdot d^{-1}$ for 14 d to 5 $g \cdot d^{-1}$ for 7 d) resulted in an increase in high-intensity, intermittent exercise performance in seven patients with mitochondrial cytopathy (101). In a subsequent study, this group found that a similar Cr supplementation strategy resulted in enhanced muscle performance in an open ($N = 81$) and single-blind trial ($N = 21$) in patients with a variety of neuromuscular disorders (100). Thus, Cr supplementation may have a place in managing patients with muscular and/or neuromuscular disorders.

Stroke/neurodegenerative disease. Creatine promotes glutamate uptake into synaptic vesicles (118), which may lead to a reduction in neural glutamate excitotoxicity. Creatine results in less energy impairment in anoxic hippocampal slices (12). Creatine supplementation (1 and 2% of diet) attenuated oxidative stress and neuronal drop-out in a rodent model of Huntington's disease (58). This same research group also found that a similar Cr supplementation protocol resulted in an attenuation of alpha-motor neuron drop-out and an improved survival in a transgenic murine model of familial ALS (G93A Cu/Zn SOD mutant) (52). There is no direct evidence available in animal or human stroke models.

Postoperative surgical recovery. Inadequate food intake (e.g., absence for surgery; cachexia; etc.) and muscle atrophy are common in patients with orthopedic surgical procedures and immobilization. Tempering of muscle atrophy in such situations could facilitate rehabilitation. Long-term Cr administration to patients with Type II muscle fiber atrophy resulted in a 43% increase in fiber diameter after 1 yr of supplementation (91); this benefit was subsequently maintained for up to 5 yr (111). A single study has demonstrated enhanced recovery of leg strength after knee surgery in the group given 1 $g \cdot d^{-1}$ of PCr intravenously over 1 month, as compared to a control group (89).

Does the Apparent Absence of Health Risks Make Cr Supplementation Safe and Appropriate?

As with ingestion of any compound in excess into the body, there are a number of aspects that should be recognized. The fact that Cr is a naturally occurring compound does not make supplementation safe, as numerous compounds are good, even essential in moderation, but detrimental in excess. Further, the lack of adverse effects does not equal safety, since unending research must be performed to eliminate the possibility of all theoretical complications.

As with any nutraceutical preparation that is not subject to a certification process such as conducted by the FDA, purity and safety are not assured.

Even if completely safe, it is important to pose some questions: Is Cr supplementation appropriate in the sports venue? Why attempt to enhance sport performance by external means when athletic skill, dedicated training, and personal effort remain the stellar qualities of true athletic competition? Certainly any view that ergogenic agents are essential to achieve the "competitive edge" in sport events undermines the spirit of athletic competition. Such a view may even foster a misguided drive that more is better and/or external dependence is essential. These comments, of course, apply to any ergogenic agent that is not presently regulated.

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