Creatine Monohydrate

To supply an NSF Certified for Sport (NSFCS) superior creatine supplement in its most clinically successful monohydrate form using the raw material, Creapure®, (a pure creatine monohydrate made in Germany), to maximize the well-known size and performance enhancing effects of creatine supplementation. This patented raw material helps creatine remain stable during digestion, thus making it almost fully available to the body. Proper dosing of dotFIT's CreatineMonohydrate may improve the ability of creatine supplementation to enhance training outcomes in various sports and types of exercise when compared to equal amounts of other creatine products.
The goal of supplementing creatine monohydrate (CM) is to increase the muscle levels of creatine and speed the regeneration of creatine phosphate (PCr) beyond what can practically be accomplished by diet alone. Creatine loading is much like the goal of carbohydrate loading by endurance athletes, but instead of increasing glycogen storage, and thus delaying glycogen depletion, loading creatine would enhance PCr levels and delay its depletion and speed repletion. This practice would benefit strength and power activities that are dependent on PCr as an energy source, including sprinting and weightlifting. Other sports that also require repetitive bursts of speed and power – i.e. specific intermittent athletes (team sports – i.e. combined intermittent aerobic and anaerobic activity such as football, baseball, rugby, hockey, etc.) could also benefit from creatine supplementation.
Note: *The dotFIT powdered form of CM allows the user the freedom to conveniently and accurately control delivery and dosage throughout the day. Additionally, because it's a single ingredient product, dotFIT CreatineMonohydrate is ideal for increasing total creatine intake to desired levels when using other creatine products that contain mixed ingredients with limited dosage recommendations (see Mix Dosing & Stacking instructions in Appendix).*

Rationale

Creatine (Cr) is an amino compound found in skeletal, cardiac, and smooth muscle that plays an indispensable role in energy metabolism in these tissues.[1] The phosphorylated form, creatine phosphate (PCr), provides an immediate energy source for the brain and muscles and therefore, the primary rationales for supplementation are to increase, replete and prolong this energy source.[1]

Function and Metabolism

Endogenous production of creatine occurs in the liver, kidneys, and pancreas from the amino acids methionine, glycine, and arginine (folate and vitamin B 12 are also catalysts).[2,3,4] Most of the total body creatine resides in skeletal muscle (SM) where about one-third exists as creatine (Cr) and two-thirds as phosphocreatine (PCr). Depending on muscle fiber type and total mass, an average 150 lb male has a creatine pool of approximately 120-140 g.[5,6] Typically, the human body manufactures about one gram/day of creatine, obtains one gram from food (muscle meats contain ~300-500 mg per 100 g serving), and loses about two grams per day. Therefore, under normal circumstances, creatine levels are fairly constant.[7,8]
Creatine synthesized in the liver is released into the bloodstream and taken up into muscle and brain cells through the sodium-chloride dependent creatine transporter (SLC6A8) or better known as Crea T1.[9] Creatine can then be phosphorylated by creatine kinase during times of sufficient ATP availability.[1,2] Creatine uptake is synergistically regulated by various mechanisms such as current phosphorylation and glycosylation along with the extracellular and intracellular levels of creatine. Crea T1 is particularly sensitive to the extracellular and intracellular levels and directly activated when total creatine content inside the cell decreases.[10] Aside from cellular cytosolic creatine, there also appears to be a mitochondrial isoform of Crea T1, which allows creatine to be transported into the mitochondria suggesting an intra-mitochondrial pool of creatine that may be a key factor in the phosphate-transport system from the mitochondria to the cytosol.[10,11] Creatine uptake appears to be enhanced by insulin[12,13,14,15] and triiodothyronine.[16] Without supplementation, the average concentration of total Cr in skeletal muscle varies between 45 and 68 mmol/lb dry weight in normal humans (or 0.3-0.5% of muscle weight).[6,7] Supplementation has been shown to increase SM total

creatine content >15% and up to 24%[15], and >9% in the brain.[1,17,18] Cr and PCr are degraded to creatinine in a non-enzymatic and irreversible reaction.[2,4] Creatinine is then filtered by the kidneys into the urine, the primary route of loss.[2] Since the production rate of creatinine is fairly constant, creatinine plasma concentrations are used as a clinical measure of glomerular filtration rate (GFR) or kidney health. Very high creatinine concentrations indicate diminished filtration function and renal failure. However, users of creatine supplementation being tested in this manner, because of harmless excess creatinine presence, can give a false reading that readily clears up after cessation of oral ingestion of creatine (see creatine and safety section below).[19]

Mechanisms of Action

The predominate food sources of creatine are animal muscle meats, adding to the impractical ability to use foods to saturate muscle creatine stores for the goal of increasing performance, size, or other known potential supplementation benefits.[25] PCr, with its high-energy phosphoryl transfer potential, serves to maintain intracellular adenosine triphosphate (ATP) levels.[20] At rest, concentrations of ATP, PCr, and Cr in skeletal muscle are 4, 25, 13 mM, respectively.[5,6] During exercise, levels of ATP decline very little until stores of PCr are used.[21] Since creatine supplementation has been shown to increase intracellular levels of PCr, intracellular levels of ATP may be maintained at higher levels for longer periods of time.7[,22,23] Therefore, the aim of creatine loading with supplementation is much like the goal of carbohydrate loading by endurance athletes, but instead of increasing glycogen storage, and thus delaying glycogen depletion, loading creatine would enhance PCr levels and delay its depletion while accelerating repletion. This practice would primarily benefit activities that are dependent on PCr as an energy source such as sprinting and weightlifting. However, due to the ability of creatine to increase the muscle buffering capacity (neutralizing lactic acid), creatine supplementation may also help support the glycolytic energy system thus offer greater overall energy potential to athletes in sports other than just those involved in high intensity activities that continuously stop and start.[15,24] To be sure, the majority of studies focusing on creatine supplementation report an increase in the body's creatine pool,[25,26,27,28] with exercise increasing the uptake and leading to an increase in exercise performance during anaerobic activities.[25,28] Early research by Volek et al.[29] attributed the increases in strength performance, after 12 weeks of creatine supplementation with exercise, to an increased total creatine pool resulting in more rapid ATP regeneration between exercise sets, allowing athletes to maintain a greater training intensity and improve the quality of the workouts throughout the entire training period. Additionally, creatine supplementation has been shown to cause a reduction in plasma concentrations of hypoxanthine and lactate following exercise, suggesting lower levels of anaerobic glycolysis, another possible contribution to delaying muscular fatigue by attenuating the exercise induced decrease in muscle pH.[30] Because of creatine's aforementioned functions in the body (see Figure 1), supplementing creatine to maximize stores thus strength, size, and/or performance, has become one of the most popular and heavily researched nutritional supplement protocols.[25,31,32,33,34]

Creatine supplementation (CS) with exercise clearly improves many training outcomes such as activity specific physical performance and skeletal muscle size and development,[25,32,33,35,36,37,38] through at least one obvious mechanism of action described above. The ability of CS to raise the muscle content of PCr significantly increases anaerobic capacity and can lead to improved training bouts that can build on each other.[26,27,28,29,39] CS may also work through other unique muscle building/recovery/development mechanisms of action during the supplementing phase.[26,40,41] These more recent elucidated mechanisms of CS may include changes in gene expression,[40,42] satellite cell proliferation, insulin-like growth factor signaling,[27] increase in growth hormone,[41] alterations in myogenic transcription factors leading to a reduction in serum myostatin (muscle growth inhibitor),[43] improved neuromuscular function (facilitating the reuptake of Ca^{2+} into sarcoplasmic reticulum),[44] and as mentioned above,[30] reduced exercise induced blood lactate.[45] Finally, CS may also participate in reducing muscle damage from high intensity resistance training and endurance exercise.[46]

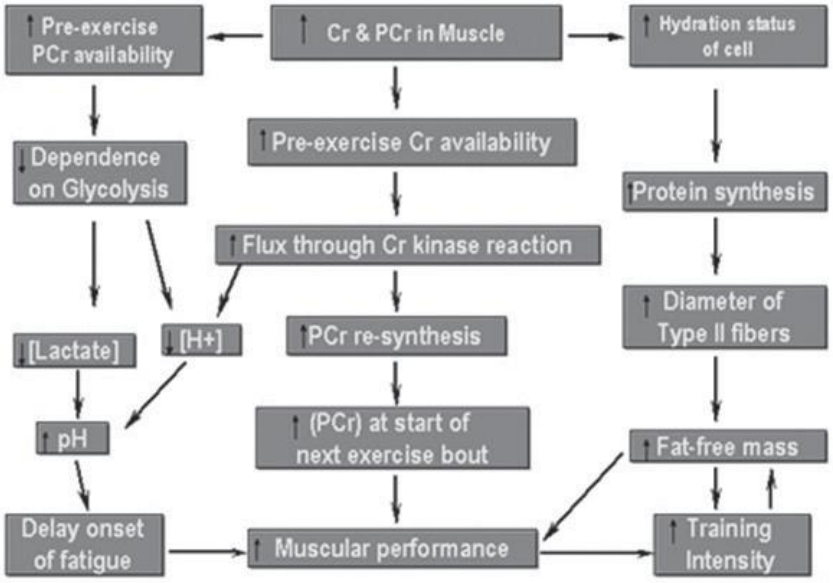

Figure 1: Impact of creatine on high-intensity exercise (adapted from Volek and Kraemer with permission).

Creatine Supplementation

Note: *unless otherwise noted, all studies cited used supplemental creatine in the monohydrate form, (CRM) and at this time, it is the only form recommended for use*.

Creatine and Anaerobic Exercise Performance

During anaerobic activities, the split of ATP production between PCr utilization and glycolysis depends on the intensity and duration of the activity. During the first 3 seconds of intense contractions, PCr breakdown supplies up to 70% of needed ATP.[47] Therefore, the proportion of anaerobic ATP production delivered by PCr will be greatest at the onset of exercise but after ~ 6 seconds of continuous activity, glycolysis will deliver a greater share of ATP.[48] However, PCr is rapidly re-synthesized during rest. In fact, 50% of the depletion may be restored after ~30 seconds.[49] Removal of muscle lactate is much slower with ~50% of accumulated lactate cleared in ~10 minutes.[24]

In summary, during high intensity interval activities with short rest periods, PCr will provide the main source of anaerobic ATP. As described above, CS significantly increases PCr stores and decreases repletion time while delivering a lactic acid buffering effect, giving proper CS great potential for athletes performing high intensity anaerobic activities and related sports to improve performance or training outcomes when compared to a non-supplemented state.[25]

Anaerobic Creatine Supplementation Studies in Athletes, Exercisers & Older Adults

Overview

CS and resistance training was shown in a 2003 meta-analysis to produce an 8% increase in performance in 1 repetition max (RM) and a 14% increase in reps per set.[33] The Branch et al. meta-analysis showed an overall effect size (ES) of creatine supplementation of 0.24. This group of studies showed a 7.5% improvement from baseline vs. 4.3% in placebo on primarily anaerobic exercise (activities ≤30 seconds which primarily utilize the ATP-phosphocreatine system).[32] Later reviews confirmed similar findings across different anaerobic activities.[35,41,45] The meta-analysis by Lanhers C et al. on lower limb strength included 60 studies (646 subjects in CS group and 651 controls). At the end of

CS period, the effect size for squat was 0.336, leg press 0.297, and 0.266 for overall quadriceps. The authors concluded CS was not only effective in lower limb strength performance for exercise with a duration of less than three minutes, but also that results were independent of subject characteristics, training protocols, and supplement doses and duration.[50] CS also demonstrates performance and lean mass increases in older male and female adults.[51,52]

Other Related Studies

- Tarnopolsky et al. in a double-blind placebo controlled manner, administered five grams of Cr four times per day for four days and measured anaerobic cycle performance, plasma lactate, dorsi-flexor maximal voluntary contraction (MVC), 2-minute fatigue test and electrically stimulated peak and tetanic torque; isokinetic knee extension torque and 1-min ischemic handgrip strength. The authors found "Significant main effects of Cr treatment included increased peak and relative peak anaerobic cycling power (3.7%), dorsi-flexion MVC torque (6.6%), and increased lactate (20.8%;) with no gender specific responses." They concluded that short-term Cr supplementation can increase measures of high-intensity exercise performance in males and females.[53]
- Dabidi et al. used 20 g per day of CS for six days vs. placebo, and evaluated muscle fatigue and physiological indices after intermittent swimming bouts in 16 trained swimmers. The swimmers performed six repeated sprints of 50 meters departing every 120 seconds. Blood lactate, Creatine Kinase (CK), creatinine, heart rate, best repeated sprint (RSb) and mean repeated sprint (RSm) times, and percentage of speed decrement (%Dec) were measured at different phases of bouts. The results showed that CS improved swimming performance and reduced blood lactate levels following intermittent sprint swimming bouts. The authors concluded "CS in trained swimmers may improve anaerobic performance and heart rate variations independent of the effect of intensive sprint swimming bouts."[45]
- Interestingly, Manjarrez-Montes de Oca R, et al. found using an unusually low dose of ~3.5 g/day in Taekwondo practitioners to slightly increase fat mass and serum triglycerides concentration without improvement in anaerobic power. The study design would be considered weak on many fronts, but it does reinforce the idea that CS is not for all types of athletes that participate in predominately anaerobic activities.[54] On that note, Schubert et al. in a systematic review of ergogenic aids for improving running performance in both middle (400-5000 m) and long distance 10,000 m marathon), found only sodium bicarbonate (middle distance), caffeine and carbohydrate supplementation to be significantly effective.[55] Additionally, Williams et al. found no significant differences between placebo and 20 g/d for seven days of CS in measures obtained during a 90-min soccer-simulation test, thus bringing into question its potential as an effective ergogenic aid for soccer players.[56]
- Camic et al. examined the effects of a relatively low dose of a novel form of CS for 28 days. They administered 1.25 and 2.5 g of CS polyethylene glycosylated creatine (PEG-creatine) to test anaerobic performance measures (vertical and broad jumps, 40-yard dash, 20-yard shuttle run, and 3-cone drill), upper- and lower-body muscular strength and endurance (bench press and leg extension), and body composition. The results showed improvements in vertical jump, 20-yard shuttle run, 3-cone drill, muscular endurance for bench press, and body mass for at least one of the PEG-creatine groups without changes for the placebo group. Authors concluded that PEG-creatine supplementation at 1.25 or 2.5 g/d had an ergogenic effect on lower-body vertical power, agility, change-of-direction ability, upper-body muscular endurance, and body mass.[57]
- In another study that further highlights the complexity identifying athletes in specific sports or training protocols where CS would be useful, Joao G Claudino et al. takes a different approach on use for soccer athletes. They examined the effects of creatine supplementation versus placebo on lower-limb muscle power in Brazilian elite soccer players during early phase preseason training period where training loads are intensified and often contribute to functional overreaching. The hypothesis was that CS would attenuate the small but significant decline in lower-limb muscle power performance during this phase of training. The creatine group consumed 20 g/d of creatine monohydrate for one week divided into four equal doses, followed by single daily doses of five grams for the next six weeks. They observed a performance decline in the placebo participants, but not in the

creatine group, and concluded "CS prevented the progressive training-induced decline in lower-limb performance in professional elite soccer players during pre-season."[58]

- Another positive CS soccer application was found by Camillo et al. They used 20 g/day (four doses of 5 grams) for the first week (loading) and five grams thereafter for five weeks versus placebo in female soccer players to investigate a six-week plyometric training and CS intervention on maximal-intensity and endurance performance during in-season training. After intervention, the control group didn't change, while both plyometric training groups improved jumps (ES = 0.25–0.49), sprint (ES = 0.35–0.41), repeated sprinting (ES = 0.48–0.55), endurance (ES = 0.32– 0.34) and change-of-direction speed performance (ES = 0.46–0.55). However, the CS participants improved more in the jumps and repeated sprinting performance tests than placebo groups. The authors concluded that the plyometric training was effective by itself but also demonstrated that creatine supplementation during plyometric training significantly enhanced adaptations related to maximal-intensity exercise and repeated sprint ability compared to placebo.[59]
- Ziegenfuss et al. used a supplement containing CM which was administered 10 g/d for two weeks followed by 5 g/d for the final two weeks and tested golf driving distance. They found that 30 days of CS significantly improved best drive distance more than placebo.[60]
- Using creatine malate supplementation (CML) for six weeks including a loading phase, Tyka et al. found significant ergogenic effects in sprinters reflected by the increase in anaerobic exercise and morphological indices, and in long distance runners. The supplemented group of sprinters also had elevated growth hormone levels compared to all other groups after graded exercise testing. The significant increase in the distance covered during graded testing was only demonstrated in the CML group of long-distance runners, presumably from a delayed anaerobic threshold appearance during the exercise test to exhaustion. This latter result may speak to the potential of CS in endurance activities.[61]
- In the same vein as Tyka et al., de Andrade et al. showed a five-day CS load increased the anaerobic energy contribution during 1K cycling time trial and resulted in a higher body mass of the subjects compared to placebo, but no time difference in completing the trial (increase in weight may have been a factor). The conclusion was that Cr loading slows the VO_2 response and increases the anaerobic contribution during a 1-km cycling time trial. This effect suggests that CS may potentially help delay fatigue in shorter event aerobic activities.[62]
- Havendtidis et al. reviewed 21 studies of military personnel using creatine and found only three of nine exercise protocols used during randomized clinical trials showed a significant performance enhancing effect. However, because of the wide success of CS in the general population as demonstrated in over 100 other clinical trials, the authors surmised that limitations in creatine dosage, military fitness testing and sample group selection might have underestimated the ergogenic properties of creatine.[63]
- Zuniga et al. used a randomized, double-blind, placebo-controlled design, to study the effects of seven days of CS with 20 g/d on mean power (MP) and peak power (PP) from the Wingate anaerobic test, body weight (BW), 1-repetition maximum (1RM) bilateral leg extension (LE) strength, and 1RM bench press (BP) strength. The results showed a significant increase from the pre-creatine test to the immediate post-creatine testing in MP for the CS subjects (5.4%) but not for the placebo group (-0.3%). However, seven-days of CS had no significant effect on 1RM, LE and 1RM BP, PP or BW.[64] The short duration of the study probably played a role in the limited latter results.

Older Adults

- Baker et al. had healthy aging males (average 55 years) consume CS (20 g) and placebo, on two separate occasions (seven days apart), 3 hours before performing leg and chest presses repetitions to fatigue (3 sets at 70% 1-repetition maximum; one minute rest between sets). They found that a "bolus ingestion of creatine consumed three hours before resistance exercise has no effect on upper or lower-body muscle performance in healthy aging males".[65] This dosing protocol is probably a good picture of how not to use creatine.

- Contrary to Baker et al. above, Johannsmeyer et al. used a known effective dosing protocol (0.05 gm/LB/day of creatine or placebo for 12 weeks), examined CS in untrained aging adults on drop-set resistance training. Seven females and 10 males aged 57.6 ± 5 years performed the following protocol: 3days/week; 2 sets of leg press, chest press, hack squat and lat pull-down exercises performed to muscle fatigue at 80% baseline 1-repetition maximum (1-RM) immediately followed by repetitions to muscle fatigue at 30% baseline 1-RM. The CS group significantly increased body mass and muscle mass compared to placebo. Males using CS increased muscle strength to a greater extent than females on CS. CS enabled males to train at a greater capacity over time compared to males on placebo. The authors concluded that "the addition of creatine to drop-set resistance training augments the gains in muscle mass from resistance training alone and CS is more effective in untrained aging males compared to untrained aging females."[66]
- Candow et al. conducted a randomized placebo controlled trail comparing the effects of CS before vs. after supervised resistance training (RT) performed 3-days/week in healthy older adults using .05 g/d of CS over 12 weeks (~8 g/d). Results showed compared to placebo, both CS groups experienced a significant increase in whole-body lean tissue mass, limb muscle thickness, and upper and lower body strength and a decrease in muscle protein catabolism, with no differences between CS groups. Additionally, there was no change in kidney function throughout the trial. The conclusion was that "changes in muscle mass or strength are similar when creatine is ingested before or after supervised resistance training in older adults."[67]
- Lanhers et al. conducted a systematic review and meta-analysis of all randomized controlled trials comparing CS with placebo on strength performance in exercises shorter than three minutes in duration to determine the effect of CS on upper limb strength performance. They included 53 studies (563 individuals in the creatine supplementation group and 575 controls). The effect size (ES) compared to controls for bench press and chest press were 0.265 and 0.677, respectively. Overall, pectoral ES was 0.289 and global upper limb ES was 0.317. Meta-analysis of changes between baseline and end of supplementation gave similar results. The authors found the meta-regression showed no link with characteristics of population or supplementation, demonstrating the efficacy of creatine independently of all listed conditions. Their conclusion: "CS is effective in upper limb strength performance for exercise with a duration of less than three min, independent of population characteristics, training protocols, and supplementary doses or duration."[68]

Creatine and Hypertrophy

Along with increasing performance, CS generally consisting of a loading phase 20 g/d [.14g/lb/d] and a maintenance phase of 3-5 g/d [.02-.03g/lb/d], has also been shown to produces greater gains in exercise induced muscle hypertrophy compared to placebo.[25,32,36,69,70]

Hypertrophy Related Creatine Supplementation Studies in Athletes, Exercisers & Older Adults

Overview

Looking at contributing factors to the loss of muscle mass in humans including satellite cell activity,[27,71] changes in muscle morphology,[72] hormonal production and kinetics,[27,41,43] oxidative stress,[73] and under or untreated muscle damage from exercise or other forces,[46,74] the mechanisms in which CS may help offset this loss or contribute to hypertrophy are brought to light.[75] Safdar et al. found CS to effectively influence gene expression and muscle protein signaling pathways.[40] Vierck et al. found creatine administration in vitro to induce differentiation of myogenic satellite cells.[76] Later work by Olson et al. confirmed CS contribution to satellite cell proliferation and the mononuclei number in skeletal muscle induced by resistance training.[77] CS has also been shown to increase blood flow to exercising muscles and raise anabolic hormones such as growth hormone and IGF-1 involved in muscle hypertrophy.[41,43,61,69] And finally, the obvious mechanism related to CS and hypertrophy is the increase in exercising performance (all described above) that leads to enhanced training sessions that continue to build on each other over time.[29] Antonio et al. demonstrated that five grams of CS daily taken only pre-workout in one group and five grams taken only after

workouts in the other group for four weeks (five grams taken anytime on non-workout days) led to significant increases in lean body mass in both groups (2.1 lbs in the pre-group and 4.4 lbs in the post).[78] This study also suggests that CS post exercise may be more important than solely in the pre-exercise period. In a study that measured cross sectional area changes, Cribb et al. used six grams before and after exercise for 10 weeks and found greater increases in lean tissue mass and cross-sectional area of type II fibers[70] (see Figures 2-4).The Branch et al. meta-analysis (100 peer-reviewed studies) showed an overall effect size (ES) of CS on body composition of 0.17-0.26 depending on loading protocol, maintenance dosing, and exercise type and duration. The authors concluded: "ES was greater for changes in lean body mass following short-term CS, repetitive-bout exercise tasks ≤ 30 s (e.g., isometric, isokinetic, and isotonic resistance exercise), and upper-body exercise."[32]

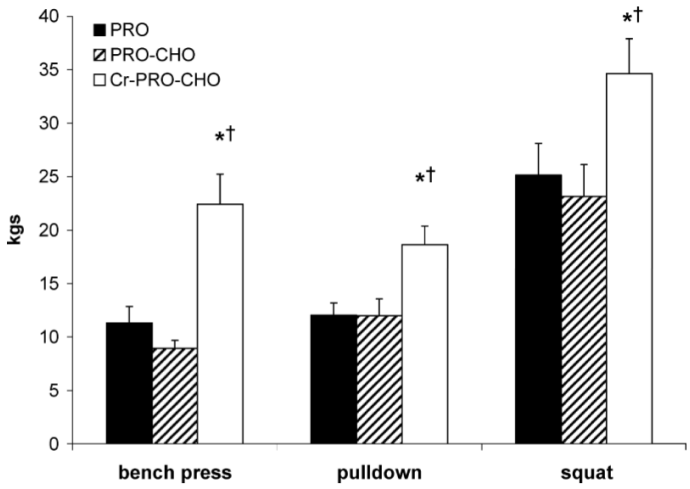

Figure 2: Adopted from Cribb et al.[70] Changes in 1 RM with the Cr-PRO-CHO group gaining significant increases compared to other groups.

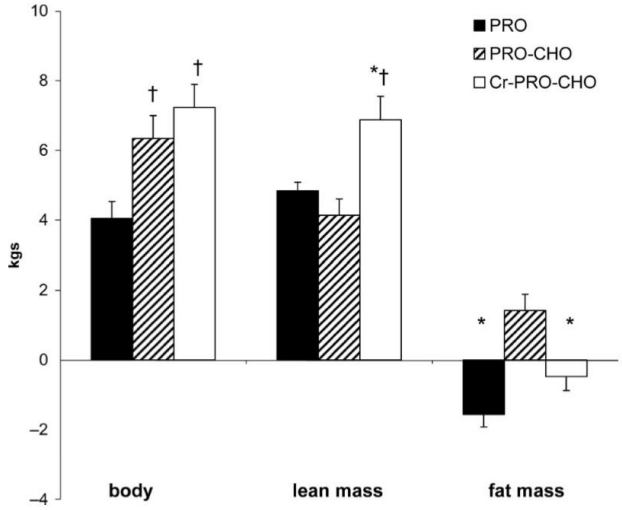

Figure 3: Cr-PRO-CHO and PRO-CHO groups with significant differences body mass and composition than PRO only group. Adopted from Cribb et al.[70]

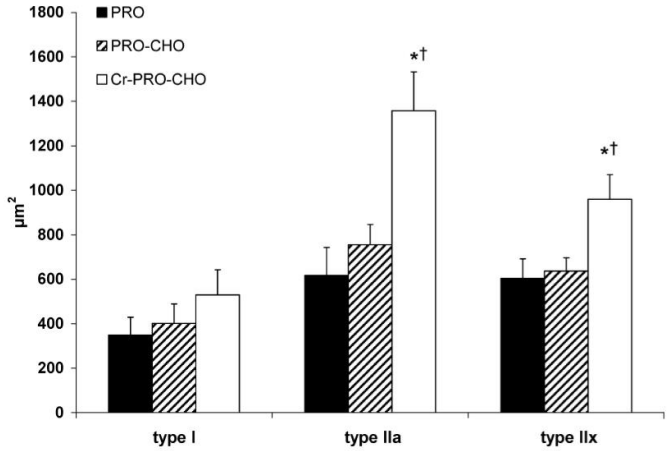

Figure 4: Cr+PRO+CHO group showed significant increases in muscle fiber CSA compared to other groups without creatine. Adopted from Cribb et al.[70]

Other Related Studies

- Candow et al. found similar results to Antonio et al. in the fact that CS may be more beneficial immediately post exercise versus pre-exercise alone, at least if using CS in a single daily dose. Candow et al. studied older adults (50–71 years) randomized to one of three groups. Group 1 took creatine (0.05gm/lb) immediately before (CB) resistance training (RT) and placebo immediately after (0.05 g/lb cornstarch maltodextrin); Group 2 did the reverse of group one (CA); Group 3 consumed a placebo before and after (P) RT for 32 weeks. Results were an increase over time for lean mass (LM) and muscle strength and a decrease in fat mass. CA resulted in the greatest improvements in LM (6.6 lbs) compared with PLA (1.1). CS, regardless of timing of ingestion, increased muscle strength more than placebo. Leg press: CB 80 lbs; CA 90 lbs; P, 12.3 lbs; chest press: CB 33 lbs; CA 35 lbs; P 4 lbs. The authors concluded that "compared with resistance training alone, CS improves muscle strength, with greater gains in lean tissue mass resulting from post-exercise creatine supplementation.[75]
- Pinto et al. performed a 12-week, parallel-group, double-blind, randomized, placebo-controlled trial using CS (5 g/d taken after workout and 5 g after lunch on non-workout days) or placebo combined with RT. They measured primary outcomes of lean mass and strength with secondary outcomes including the lumbar spine, right and left femoral neck, both femur and whole-body bone mineral density (BMD), and whole body bone mineral content (BMC), assessed by DXA. The CS group had significantly greater gains in lean mass versus P (4 lbs vs. 1.3). However, changes in the 10RM tests for bench and leg press exercises, body composition, BMD, and BMC of all assessed sites did not significantly differ groups. The non-result factor in the secondary measured outcomes may be age and/or dose (relatively low CS dose) related. The authors conclusion was "12-weeks of low-dose creatine supplementation associated with resistance training resulted in increases in lean mass in the elderly."[79]

Creatine and Primarily Aerobic Exercise

Very little has been studied or benefits quantified using CS in aerobic activities due to CS targeting the ATP-phosphocreatine energy system. If there is a benefit, it is probably related to a change in energy substrate utilization (when PCr levels are augmented by CS), at least during the early phase of aerobic activity that might help decrease time to exaustion.[32] To be sure, the coupling between PCr and VO_2 kinetics is well documented.[15,80,81]
Roberts et al. found CS to augment muscle glycogen stores post exercise to potentially enhance the next bout or endurance activities.[15] And finally, another mechanism in which CS may indirectly benefit aerobic activities is the ability of creatine to attenuate cardiovascular and thermoregulatory responses during prolonged exercise in the heat.[82,83]

Aerobic/Endurance Related Creatine Supplementation Studies in Athletes & Exercisers

Overview

The potential of CS to positively impact substrate utilization during the early phase of shorter aerobic activity appears to be supported by de Andrade et al. as described above. They found CS slows the VO2 response and increases the anaerobic contribution during a 1-km cycling time trial.[62] Also supporting this theory, Chwalbinska-Moneta et al. observed a decrease in blood lactate accumulation and an increase in lactate threshold in elite rowers with five days of CS, suggesting a potential to improve overall performance.[84]

In another aerobic related application, de Salles et al. used a 20 g/d loading phase and 5 g/d maintenance phase and found only the CS group could maintain leg-press performance after the intermittent aerobic exercise, while the placebo group showed a significant decrease in leg-press.[85] CS significantly increased bench-press after aerobic exercise modes, while the bench-press was not affected by either mode of aerobic exercise in the placebo subjects. These results suggest acute decreases in strength following aerobic exercise may be offset by CS.[85] At this time, experimentation with CS and aerobic exercise has produced little benefit but has so far shown no downside, and may be of use to cross training athletes.

To achieve maximum glycogen storage through super-compensation, carbohydrate loading is a successful ergogenic practice in endurance sports,[86] and CS has been shown to further augment post-exercise muscle glycogen storage during carbohydrate loading in clinical trials.[15,87,88] The proposed mechanisms behind CS augmenting glycogen storage include 1) creatine induced increase in post-exercise insulin release and/or an increase in muscle insulin sensitivity;[15] 2) creatine induced muscle water retention because cell swelling can lead to an increase in muscle glycogen synthesis;[89] 3) muscle glycogen depletion increases muscle 5'AMP activated protein kinase (AMPK) activation and therefore it's possible that any Cr-mediated changes in exercise-induced AMPK activation could also modify post-exercise muscle glycogen storage.[15] The PCr/Cr ratio is known to modify AMPK activity and CS dramatically increases this ratio.[90]

Other Related Studies

- Tan et al. measured total body water (TBW), branched chain amino acids (BCAAs), lactate, free tryptophan (F-TRP), uric acid, and hypoxanthine in endurance athletes performing 60 minutes of running at 65–70% maximal heart rate and 2×100-meter sprint trials pre-and post-15 days of CS. As expected, creatine loading increased body weight (BW) in all participants. They also found reduced post exercise plasma lactate and the F-TRP/BCAA ratio and increased urinary hydroxyproline concentration. These endpoints combined with the tendency for purine metabolites (the sum of hypoxanthine and uric acid), urinary 3-methylhistidine, glutamine and urea nitrogen concentrations to decrease before the running trials with CS, led the authors to conclude that CS may reduce muscle glycogen and protein breakdown in aerobic and anaerobic activity.[91]
- Kilduff et al. found the hydrating effects of creatine loading to positively influence the thermoregulatory, metabolic and cardiovascular responses during prolonged exercise in heat in endurance-trained athletes.[92]
- Roberts et al. used 20 g/d of CS for seven days and found CS to dramatically augment post-exercise muscle glycogen storage above placebo during a standard carbohydrate loading protocol, and this augmentation of glycogen storage took place almost completely within the first 24 hours of supplementation. The magnitude of glycogen re-synthesis during the first 24 hours of supplementation was ~82% greater in the CS subjects compared to placebo (CS 410 ± 50 vs. placebo 225 ± 50mmol kg−1 dry muscle).[15]
- Rahimi et al. investigated seven days of 20 g/d of CS on its ability to ameliorate apoptosis induced by aerobic exercise (AE) to exhaustion in young athletes by measuring serum p53 (p53 plays a major role in oxidative stress induced apoptosis through directly regulating the expressions of pro-oxidant and antioxidant genes or through modulating the cellular metabolic pathways) and insulin-like growth factor-1 (IGF-1) concentration. They found plasma p53 levels were significantly decreased after CS with no effect in the placebo treatment. Therefore, as decreased p53 levels indicate a decrease in apoptosis and oxidative damage to DNA, these results suggest that CS

may decrease the risk of oxidative damage to DNA and concomitant apoptosis. The authors concluded "CS, which attenuated p53 protein, may lead to inhibition of p53 signaling event and subsequently promoted cell survival and protected the cell from oxidative stress. The decrease in p53 levels and increase in IGF-1 levels infers that short-term CM supplementation induced a protective effect on apoptosis," suggesting there may be a recovery benefit for endurance athletes.[93]

Creatine and Muscle Recovery from Exercise Damage or Injury

CS has been shown to improve recovery from injury,[94] muscle damage (post-exercise ingestion may enhance the regenerative process by improving the anabolic environment)[95,96] and ameliorating oxidative stress[97] from exercise.[46]

Muscle Damage Creatine Supplementation Studies in Athletes & Exercisers

Overview

There are three basic parts to exercise induced muscle damage: 1) morphological changes in sarcomere (Z-disc, I, and A band), sarcolemma, sarcoplasmic reticulum, and cytoskeletal elements;[98] 2) Impaired calcium homeostasis resulting from sarcoplasmic reticulum dysfunction. This action is caused by the calcium-activated neutral protease, calpain-3,[99] which increases muscle damage and protein degradation;[100] 3) Obligatory inflammatory response. This generally promotes further muscle damage as macrophages and neutrophils converge on the damaged tissues to begin phagocytosis, and produce compounds that exacerbate oxidative stress.[101] Exercise induced muscle damage can lead to decreases in maximal strength, excessive delayed-onset muscle soreness (DOMS) and increases in markers of muscle damage such as creatine kinase (CK) and lactate dehydrogenase (LDH) in the blood.[46,98]

Similar mechanisms of action proposed for the effects of creatine on hypertrophy are also used to explain creatine's putative effects on muscle damage, including inflammatory response, oxidative stress, calcium homeostasis, and satellite cell activities in damaged muscle.[46] CS has demonstrated a support role in ameliorating exercise induced inflammation.[102] Santos et al. showed five days of CS at 20 g/day used before 34 marathon runners competed, significantly reduced LDH, prostaglandin E_2 (PGE_2), and tumor necrosis factor-a (TNF-α) after the 30 km race compared to placebo.[102] Other studies have found similar results using similar protocols in the reduction of inflammatory markers.[73,95,103,104] The potential importance of this reduction in the inflammatory response from CS is that it indicates a decrease in exercise induced damage to the sarcolemma, and therefore leading to enhanced recovery before the next exercise bout.[105]

The role of creatine supplementation in reducing oxidative stress is another potential mechanism involved in the reduction of exercise induced muscle damage.[93,106,107] Rhaimi et al. found taking CS for seven days at 20 g/d, reduces malonyldialdehyde (MDA) and 8-hydroxy-2-deoxyguanosine (8-OHdG) levels after resistance training when compared to placebo. Other studies have come up empty on CS reducing oxidative stress.[108]

Creatine plays a role in supporting the sarcoplasmic reticulum calcium pump function through creatine's phosphorylation of ADP to ATP[96] and leading to decreased cytosolic calcium levels[99] and more rapid recovery of ATP homeostasis, which may help ameliorate secondary muscle damage caused by high calcium concentrations.[109]

A last proposed mechanism for the role of CS in muscle damage may be its purported effect on satellite cell (SC) proliferation since SCs play an important role in muscle regeneration.[110] Most telling, Safdar et al. used 20 g/d for a three day load and 5 g/d for seven days, and found CS compared to placebo "promotes proliferation and differentiation of satellite cells and activates cytoskeletal remodeling genes."[40]

Other Related Studies

The reader is referred to the review by Jooyoung et al. "*Role of Creatine Supplementation in Exercise-induced Muscle Damage: A Mini Review"* for a detailed list of CS and exercise induced muscle damage. [46]

Creatine and Health

CS can improve athletic performance under many conditions, but it has also been shown to provide potential benefits to specific health conditions including improvement in neurological and cognitive function,[111,112] offer protection against muscle wasting (sarcopenia),[113] neurological disorders and trauma.[114] CS may also improve bone remodeling in the elderly population.[113]

Rawson et al.'s review on the effects of CS on cognitive function showed that higher brain creatine is associated with improved neuropsychological performance including cognitive processing, and CS protocols can increase brain creatine and phosphocreatine contents.[112] CS has demonstrated positive effects on neurodegenerative diseases that may be attributed to improved overall cellular bioenergetics due to a greater phosphocreatine pool following supplementation.[114,115] And finally, as described above, CS has demonstrated antioxidant and cytoprotective activities.[116]

Health/Brain Related Creatine Supplementation Studies

Overview

It is beyond the scope of this article to discuss in detail the potential mechanisms of action of creatine related to this category. The reader is referred to a paper by Riesberg et al. titled, "Beyond Muscles: The Untapped Potential of Creatine", for more information on actions of creatine in neuroprotection, cognitive function, or other specific health targets.[114]

CS has been studied for its neuroprotective effects because of the high levels of creatine in the central nervous system (CNS). CS has been observed in conditions such as traumatic brain injury, amyotrophic lateral disease, Parkinson's disease, Huntington's disease and other neurological conditions.[114,117] In these conditions and from increases in reactive oxygen species (ROS),[118] the mitochondrial permeability transition pore (protein that is formed in the inner membrane of the mitochondria in certain pathological conditions where it's induction can lead to mitochondrial swelling and cell death through apoptosis or necrosis) is induced causing an outflow and influx of molecules that can negatively affect osmotic balance, resulting in damage to the mitochondria.[119] The induced mitochondrial permeability transition pore (MPTP) also disrupts ATP production.[120] Therefore, it has been postulated that neuroprotection from CS happens from inhibiting MPTP induction through stabilization of mitochondrial creatine kinase and stimulating the production of phosphocreatine.[115] Additionally high levels of ATP, which CS increases, can help prevent the MPTP from being induced.[114,118,121]

Other Related Studies

- Turner et al. observed the influence of CS on the neurophysiological and neuropsychological function of healthy young adults during acute oxygen deprivation. Using CS (20 /d) versus placebo for seven days, 15 subjects increased their brain creatine on average by 9.2% and were exposed to an oxygen deficit impairing a range of neuropsychological processes. Hypoxia-induced decrements in cognitive performance, specifically attention capacity, were restored when participants were creatine supplemented, and corticomotor excitability increased. The authors proposed that the neuromodulatory effect of creatine, from the increased energy availability, was the contributing factor of the cognitive restoration by possibly supporting the maintenance of appropriate neuronal membrane potentials. They also stated," this is the first demonstration of creatine's utility as a neuroprotective supplement when cellular energy provision is compromised."[18]
- Because CS is known to exert anti-inflammatory actions on vascular endothelium and capable of lowering arterial stiffness evaluated after resistance exercise,[122] de Moraes et al. investigated the effect of CS on vascular function, specifically, the microcirculation and homocysteine levels in 40 healthy young subjects.[123] Using 20 /d for seven days they found: 1) improved microvascular reactivity; 2) increase skin capillary and recruitment; 3) reduced blood pressure with no changes in plasma homocysteine levels. Noting that Epoxyeicosatrienoic acids (EET) are signaling molecules which act as anti-inflammatory hormones relating to the cardiovascular system and kidney, the authors

stated: "It is possible that creatine supplementation somehow contributes to increased EET bioavailability and may represent an important adjuvant therapy to improve endothelial function that is depressed in several metabolic and cardiovascular diseases."

- Ellery et al. published a review on creatine and women which included studies that suggest CS may be highly beneficial for women under certain conditions such as depression, and a better understanding of CS in females is needed to ensure that creatine is used to its full advantage as a dietary supplement to optimize and enhance health outcomes for women.[124]
- Wilkinson et al. used 12-weeks of CS (standard loading and maintenance doses) versus placebo on 40 patients with rheumatoid arthritis (RA) for increasing lean mass and improving strength and physical function. The found CS increased muscle mass, but not strength or objective physical function with no reported adverse effects. They suggested that "CS may offer a safe and acceptable adjunct treatment for attenuating muscle loss and this treatment may be beneficial for patients experiencing severe rheumatoid cachexia."[125]
- Pinto et al. reviewed CS and glycemic control (glucose metabolism) with or without exercise in both animal and human studies done in the past 16 years. In both animal and human studies, CS with exercise demonstrated the greatest beneficial effects on glucose metabolism. CS alone showed positive results in only a few of the studies. The authors concluded: "Regarding human studies, considering the sample characteristics, the findings cannot be extrapolated to patients who have poorer glycemic control, are older, are on a different pharmacological treatment (e.g., exogenous insulin therapy) or are physically inactive. Thus, CS is a possible nutritional therapy adjuvant with hypoglycemic effects, particularly when used in conjunction with exercise".[14]
- The European Food Safety Authority (EFSA) has approved a health claim for CS and muscle strength in older adults.[126] Not to be confused with support statements, it should be noted that health claims for dietary supplements are few and rare, meaning there must be very strong long-term evidence before any government will allow them. Article 13.5 claim filed by the German firm states: *"Daily creatine consumption can enhance the effect of resistance training on muscle strength in adults over the age of 55".* Daily intake should be at least 3 g/d and be combined with regular resistance training of moderate intensity.

Responders, Partial and Non-responders

While the overall effect size of creatine supplementation is significantly positive as described above on predominantly anaerobic activity, some subjects demonstrate lesser improvements, which has been attributed to a number of factors such as genetics (Type II fiber populations, gene polymorphisms, etc.),[127,128] diet (vegetarian vs. omnivore),[69] and ineffective supplement protocols (daily dosages, loading, etc.).[129,130] Responders are generally people with lower initial levels of muscle creatine, relatively high proportion of type II muscle fibers, genetically wired to respond to increased levels of creatine, and maintain a proper dosing protocol throughout the training period.

Kilduff et al. suggested an estimated CS ergogenic threshold to classify responders and non-responders. Non-responders following CS are estimated to have a creatine uptake equal or less than 21-mmol/kg dry muscle weight increase in Cr concentration, and therefore responders would have a greater than 21-mmol/kg increase in creatine concentration.[92] Non-responders may make up 30% of users.[83] Lifanov et al. found football players with the AMPD1 CC genotype to have a greater response to CS as compared to athletes with the PPARG polymorphism.[127]

Dosing Protocols

The most common and successful dosing of CS is described by Buford T et al. within The Journal of the International Society of Sports Nutrition position stand on creatine supplementation and exercise.[35] The protocol starts with a loading phase of 20 g/d of creatine monohydrate (CM) or 0.14 g CM/lb/d split into four daily intakes of 5 g each, followed by a maintenance phase of 3-5 g/d or 0.014 g/lb/d (dotFIT recommends .04 g/lb/d based on experience) for the duration of the supplementation period.

Other protocols have used a daily single dose of ~3 – 6 g [26] without a loading phase, but this method might take between 21 to 28 days to produce ergogenic effects.[25,35] There is some evidence that dosing 20 g/d taken in 1 g

increments at ~30-minute intervals for five days may result in an increase in whole body retention of creatine (+13%) when compared to the above mentioned 4 x 5 g/d ingested in three hour intervals during the five days of loading.[131] Though this type of dosing may be difficult, it intuitively makes sense based on the body's ability to potentially transport and use creatine more effectively in smaller doses – i.e. analogous to a controlled release. Additionally, CS should be taken with carbohydrates (preferably fast acting to stimulate insulin) to maximize uptake.[12]

Creatine Safety

The efficacy and safety of the proper use of Creatine Monohydrate is well established.[25,35,132] CS used at 10 g/day for over five years by Parkinson's disease patients yielded no detectable adverse effects.[133]

Creatine Supplementation, Exercise and Creatinine

Background

Creatine supplementation has been commonly used successfully among exercisers and competitive athletes for the last 20 years to improve performance, recovery time and more recently to help maintain health.[25] Due to the spontaneous conversion of creatine into creatinine, diet (e.g. high in animal protein), proper use of creatine supplements and/or vigorous exercise, can often lead to a creatinine level reading at or above the normal (>1.5 mg/dL), which in healthy persons, is generally a harmless temporary result.[134] Therefore, we advise exercisers to not train or train lightly the day before a blood test and supplement users to cease supplementation 4-7 days before blood or urine tests.

Creatine Supplementation and Renal Function

Specific studies on creatine supplementation, renal function and/or safety conclude that although creatine does slightly raise creatinine levels, there is no progressive effect to cause negative consequences to renal function and health in already healthy individuals when proper dosage recommendations are followed.[135,136,137,138,139,140] Creatine supplementation is also used with success in the aging population.[25] A randomized, double blind, 6-month resistance exercise and supplementation intervention[141] was performed on elderly men and women (age >65 years) in which subjects were assigned to either a supplement or placebo group. The supplement group was given 5 g of creatine monohydrate (CM), 2 g dextrose and 6 g conjugated linoleic acid/d, while the placebo group consumed 7g dextrose and 6 g safflower oil/d. CM administration showed significantly greater effects in improving muscular endurance, isokinetic knee extension strength, fat free mass and in reducing fat mass compared to placebo. Furthermore, the supplement group had an increase in serum creatinine but not creatinine clearance suggesting no negative effect on renal function.

False Readings

The spontaneous conversion of creatine into creatinine[142] may falsely suggest decreased kidney function in creatine-supplemented individuals. Tests using serum endogenous markers, which are widely used in clinical practice, are susceptible to methodological errors.[134] For instance, serum creatinine and its derivatives are influenced by exercise[143] and dietary intake, particularly by creatine-containing foods or supplements. Upon the ingestion of creatine, one may expect an increase in serum creatinine, since creatine is spontaneously and irreversibly converted into creatinine. As such, a false positive diagnosis of decreased kidney function may occur in creatine-supplemented individuals when only serum creatinine data are taken into consideration. Previous observations/studies[144,145] support the inaccuracy of creatinine-based markers in the evaluation of kidney function in creatine-supplemented individuals. To overcome this potential drawback, the gold standard method, Chromium-ethylenediamine tetraacetic acid (Cr-EDTA) clearance, is used to accurately measure glomerular filtration rate. In the healthy individual, this method allows the proper conclusion that creatine supplementation did not affect kidney function.[134]

Author's Case Study

I had a standard blood test done after seven years of creatine use at 10 g/day. I was purposely still on CS at the time of the test with the last dosage taken early morning approximately eight hours before the test. The relevant readings were as follows:[146]

- Creatinine: 1.9 mg/dL (normal is .6-1.4)
- AST (SGOT): 39 U/L (normal is 10-37)
- GFR (Calc) mL/min/1. 73m2: 38.16 mL/min (normal >60)

Other than the above, the complete blood panel was all normal. The doctor noted from these readings that my kidneys appear functioning at less than 50%. Knowing that this was a false positive reading based on CS, we retested seven days after cessation of CS. The results were as follows:[146]

- Creatinine: 1.0 mg/dL (normal is .6-1.4)
- AST (SGOT): 29 U/L (normal is 10-37)
- GFR (Calc) mL/min/1. 73m2: 81 mL/min (normal >60)

As you can see, all tests of kidney function were within normal limits and three years later remains the same and the readings outside of the normal ranges were simply false positives based on a blood value from CS. As described above, always stop CS four to seven days before a blood test regardless of the testing method.

Creatine Myths

Schilling B et al. looked at the effects of long-term CS (0.8 to 4 years) on health markers and training benefits, and found no negative health effects, including muscle cramps or injuries.[147] In fact, despite prevailing myths, it appears CS has a positive impact on muscle cramps and dehydration,[148] as it has been used clinically to reduce muscle cramps by ~60%.[149] CS can increase total body water, reduce sweat rate, lower core body temperature and exercising heart rate.[150] Additionally, CS does not negatively affect the hydration or thermoregulation status of athletes exercising in the heat.[83,150,151]

Creatine Supplementation in Children and Teens

Pediatricians have stated that creatine supplementation is not safe for children and adolescents.[152] While there is a shortage of investigations that have been conducted using young subjects, no study has shown creatine monohydrate to have adverse effects in children. In fact, long-term CrM supplementation (e.g., four to eight grams per day for up to three years) has been used as an adjunctive therapy for several creatine synthesis deficiencies and neuromuscular disorders in children. [153,154] Considering the lack of available data on youth sports performance and CrM supplementation, dotFIT™ does not recommend that children under the age of 18 use creatine monohydrate without proper parental research and consent. The International Society of Sports Nutrition (ISSN) position stand on CS has included that post pubescent youth athletes should consider a creatine supplement under certain conditions: s/he is involved in serious competitive training, is eating appropriately for the sport, and his/her parents approve and understand the facts concerning the effects of properly supervised creatine supplementation.[25,31]

Forms of Creatine Supplementation

While there are many different forms of creatine commercially available, at the time of this writing, creatine monohydrate (CM), is the only form with sufficient safety and efficacy research to support the use of CS related to the claimed benefits named above. Other forms such as creatine salt forms (e.g. creatine malate, phosphate, magnesium creatine, creatine citrate, pyruvate, oroate, etc.) and creatine ester forms (e.g. creatine ethyl ester, creatine gluconate, etc.) appear to rely more on a marketing spin than proven efficacy. Furthermore, none have the advantage of a long history of safety (over 25 years and hundreds of studies) as with CM.[25] That said, because of the hydrophilic (capable of interacting with water through hydrogen bonding) nature of creatine,[7] it's bioavailability is limited, leading manufactures to continue to search for greater functional absorption (using less to get more into the desired target tissues). To reduce the hydrophilic properties of creatine, manufactures have esterified the molecule, otherwise

known as creatine ethyl ester (CEE).[155] Although the manufactures claimed CEE could by-pass the creatine transporter due to improved sarcolemma permeability, and thus greater muscle saturation, study results demonstrated that CEE was not as effective as CM to enhance serum and muscle creatine stores.[155] Polyethylene glycol is a water soluble polymer that can enhance the absorption of specific molecules including creatine. In fact, smaller doses of polyethylene glycosylated creatine have been shown to deliver strength benefits in the upper body similar to the benefits from greater doses of CM but without the weight gain.[57,156,157]

Galvan et al. used 3 g/d of creatine nitrate (also included a seven-day loading protocol at four times per day) found creatine nitrate (CN) at 3 g/d was well-tolerated and delivered similar performance benefits when compared to 3 g of CM (this is a very low dose for CM and not generally used). Additionally, this study, found no safety concerns. The authors stated, "however, there was no evidence that CN at recommended (1.5 g/d) or twice recommended doses (3g/d) is more efficacious than CM at the doses studied.[158] Joy et al. also found 28 days of 2 g/d of CN supplementation to be safe.[159]

Because guanidinoacetic acid (GAA) is a natural precursor of creatine, GAA has been explored as an alternative to CS.[160] In a randomized, double-blind, crossover trial, Ostojic et al. evaluated whether four weeks of GAA supplementation would be superior to creatine in raising creatine levels in healthy men. They found that GAA at 3.0 g/day resulted in a greater rise (up to 16.2%) in tissue creatine levels in vastus medialis muscle, middle-cerebellar peduncle, and paracentral grey matter, as compared with an equal amount of CM. Although this is only one study, the authors surmised that "GAA may be a preferred alternative to creatine for improved bioenergetics in energy-demanding tissues."[161]

In summary, if there is a potential advantage to different forms of creatine, it may be from enhanced solubility and bioavailability allowing slightly lower dosages than the common CM dosing necessary to increase muscle creatine concentrations to their maximum capacity. In the meantime, until many more studies are performed to determine a superior creatine form that can enhance its pharma-kinetics, CM is the form of choice for proven safety and efficacy. However, the raw material of the CM compound may be an important overall factor.

Creatine Monohydrate Raw Material

Not all raw materials for creatine monohydrate manufacturing are necessarily equal. Per dotFIT Practitioner Product guidelines, dotFIT Creatine Monohydrate contains Creapure, ® which is made in Germany where dietary supplements are tightly regulated. When comparing all other creatine raw materials, scientists found too much wasted as creatinine (harmless but also useless byproduct) not just in the raw material itself but also during digestion, meaning the availability for complete absorption was limited.[162] Creapure has been shown to eliminate that problem as shown in Figures 1 and 2 below comparing Creapure® to the impurities found in other types of creatine. In other words, more pure creatine, less creatinine.

During digestion, pure creatine monohydrate (Creapure®) remains stable and is almost fully available to the body (Figure 5).[162] Inferior raw materials or a too-rapid reduction in the amount of water during "recrystallization" results in higher amounts of creatinine, dicyandiamide, and dihydrotriazine (Figure 1) thus less creatine availability.[162] Typical analytical values for Creapure® are as follows:

- Creatine monohydrate: min. 99.95%
- Creatinine <67 ppm
- Dicyandiamide (DCD): not detectable
- Dihydrotriazine: not detectable

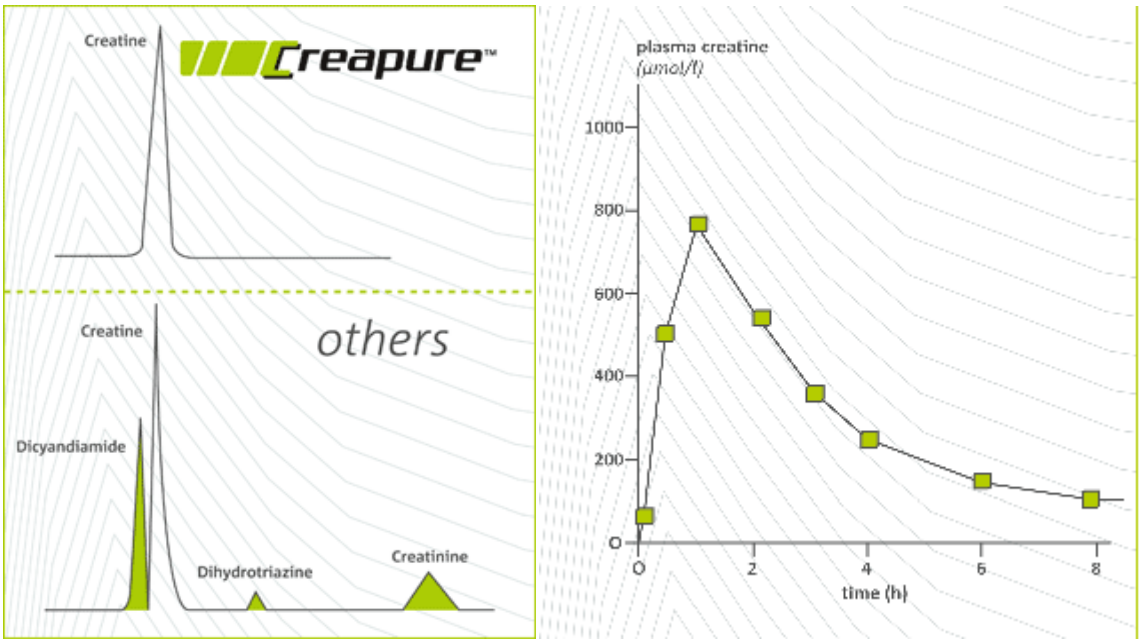

Figure 5 - One-time ingestion of Creapure® (5 grams) results in markedly elevated plasma creatine levels without raising creatinine levels[162]

Data Summary

Creatine monohydrate has been proven to be a safe and effective adult ergogenic aid. Creatine supplementation clearly benefits specific athletes and activities and because creatine is involved in energy production in almost all tissues including skeletal, cardiac and smooth muscle, CS may offer a value to most anyone.

The phosphorylated form, creatine phosphate (PCr), provides an immediately available energy source for muscles and the brain, thus the primary rationale for creatine supplementation (CS). The goal of CS is to increase the muscle (or other target tissues) levels of creatine and speed the regeneration of creatine phosphate (PCr) beyond what can practically be accomplished by diet alone to significantly enhance energy production. This practice would primarily benefit strength and power activities that are dependent on PCr as an energy source such as sprinting, weightlifting and translate to other sports that also require repetitive bursts of speed and power – i.e. specific intermittent athletes (team sports that combined intermittent aerobic and anaerobic activity such as football, baseball, rugby, hockey, etc.). Besides amplifying training outcomes, including increases in fat free mass, performance, strength, recovery and power for competitive athletes, CS has demonstrated similar results for older adults, which may lead to healthier aging and improved daily living. CS has shown some benefits in endurance/aerobic activities. These benefits are probably related to a change in energy substrate utilization, at least during the early phase of aerobic activity that might help increase time to exhaustion. Additionally, CS's well known hydrating properties may improve endurance performance during high heat conditions. And finally, CS is now being explored clinically for positive health outcomes such as improvement in neurological and cognitive function, offer protection against muscle and bone wasting (sarcopenia), neurological disorders, and trauma.

Dosing generally starts with a loading phase of 20 g of creatine monohydrate (CM)/d or 0.14 g/lb split into four daily intakes of 5 g each, followed by a maintenance phase of 3-5 g CM/d or 0.014 g/lb/d (dotFIT prefers .04 g lb/d based on experience) for the duration of the supplementation period. The length of the supplementation period would be based on the goal, but generally last 12-16 weeks and cycled throughout the year for competitive athletes.

CS used clinically or in aging populations would be decided by the attending qualified physician. Each CM dose should be accompanied with some form of carbohydrate or protein that stimulates insulin to maximize uptake. At the time of this writing, creatine monohydrate (CM) is the only evidence-based form of creatine for safety and efficacy. Young athletes who have not undergone puberty should not consider CS.

Typical Use

- All adult athletes seeking to improve training outcomes related to lean body mass, strength and power activities such as sprinting, weightlifting, jumping that also translate to other sports requiring repetitive bursts of speed and power – i.e. specific intermittent athletes (team sports that combine intermittent aerobic and anaerobic activity such as football, baseball, rugby, hockey, etc.)
- Older adults seeking healthier aging and improved daily living as recommended by a qualified physician
- Aerobic or endurance athletes to potentially delay fatigue especially under high heat conditions and assisting post exercise glycogen resynthesis

Creatine Loading & Maintenance Strategy (*Refer to Mix Dosing & Stacking Instructions in Appendix)*

- Mix one (scoop (5 g) with 4-8 oz. of favorite fluid/shake and take four times daily with a carbohydrate containing meal/drink for first five days. Thereafter take one scoop twice daily to maintain stores. To help maximize creatine uptake, split doses throughout the day with meals/drinks containing carbohydrate and/or protein (depending on size and caloric allotment)
- On training days, use one dose before workout and one after with meals/drinks. May mix with your pre/post training formula
- Dosing by body weight:
    - Loading phase 0.14 g/lb/d split into four daily intakes of 5 g each, followed by a maintenance phase 0.014 g/lb/d (dotFIT prefers .04 g/lb/d based on experience) for the duration of the supplementation period

**Programs total daily creatine first 5 days: 20 g/d. Maintenance phase: all days is 10 g. To maximize uptake, creatine intake should be spread as evenly as possible throughout the day with carb & protein containing meals or shakes*

Precautions

Creatine is a naturally occurring nitrogenous organic acid and therefore no precautions are known for healthy persons. However, as with any nitrogen containing acid (e.g. amino compounds), individuals with liver or kidney disease should avoid supplementation without supervision of a medical professional.[163] Due to lack of data regarding youth athletes, CS should be avoided at least until post-puberty. As noted above, CS often leads to weight gain from water retention and increases in fat free mass. Both these conditions are often desirable endpoints for many users.[25,89,150]

Contraindications

Although there is no supporting evidence, persons regularly using nephrotoxic drugs (drugs that harm kidney function) such as cyclosporine, aminoglycosides, gentamicin, nonsteroidal anti-inflammatory drugs (NSAIDs), naproxen and others, should not use high doses of creatine without a doctor's consent.[35,164] Persons with bipolar disorder should consult a physician regarding creatine use since there have been reports of mania in people with this disorder.[165]

Adverse Reactions

While there have been anecdotal reports of seizures, arrhythmia, ventricular fibrillation, and muscle cramps in creatine users, no scientific studies have observed these reactions.[1,25] Refer to the Creatine Safety section in this document for more information..

High doses of creatine have been reported to cause gastrointestinal distress and diarrhea in a small percentage of users, and rarely more often than placebo.[25,166] As mentioned, medical supervision is suggested for people who have kidney disease or have a high risk of kidney disease and use creatine.[164,166]

Upper Limit/Toxicity

The upper limit for creatine monohydrate has not been established.[1,163]

Summary

Purpose

To supply an NSF Certified for Sport (NSFCS) superior creatine supplement in its most clinically successful monohydrate form using the raw material called Creapure,® to maximize creatine supplementation's well known size and performance enhancing effects. The goal of supplementing creatine monohydrate is to increase the muscle levels of creatine and speed the regeneration of creatine phosphate.

Potential Beneficiaries

- All adult athletes seeking to improve training outcomes related to increasing lean body mass and improving strength and power activities such as sprinting, weightlifting, and jumping. Benefits may also translate to other sports requiring repetitive bursts of speed and power – i.e. specific intermittent athletes (team sports that combine intermittent aerobic and anaerobic activity such as football, baseball, rugby, hockey, etc.)
- Athletes with low creatine intake or biosynthesis who perform high intensity activity
- Older adults seeking healthier aging and improved daily living as recommended by a qualified physician
- Aerobic or endurance athletes to potentially delay fatigue especially under high heat conditions and assist post exercise glycogen resynthesis
- Ideal for increasing total creatine intake to desired levels when using other creatine products that contain mixed ingredients with limited dosage recommendations (*see Mix Dosing & Stacking instructions in Appendix).*

Unique Features

- Contains Creapure®, a pure creatine monohydrate made in Germany, which helps creatine remain stable during digestion rendering it almost fully available to the body, thus giving it more potential to enhance training outcomes when compared to equal amounts of other creatine products
- Convenient powdered form with relatively neutral flavoring allows for easy mixing alone or with other products such as pre/post workout shakes
- NSF Certified for Sport (NSFCS), an independent third-party test which provides an additional product guarantee to ensure purity and potency for drug tested athletes. Click here for the dotFIT NSFCS section
- Formulated and manufactured for taste and pleasing texture in a regularly inspected NSF certified facility, in compliance with Good Manufacturing Practices (GMPs) exclusively for dotFIT, LLC

Supplement Facts Label

Supplement Facts

Serving Size: 6.8g (1 heaping scoop) Servings Per Container: 60

	Amount Per Serving	% Daily Value*
Calories	5	
Total Carbohydrate	2 g	1%
Calcium	24 mg	2%
Creatine Monohydrate	5,000 mg	**

* Percent Daily Values are based on a 2,000 calorie diet.
** % Daily Value not established.

Other Ingredients: Maltodextrin, Citric Acid, Natural and Artificial Flavors, Calcium Silicate, Sucralose, Red Beet Juice (for color).

Appendix – Mix Dosing and Stacking Instructions

Adult Performance & Size Supplement Plan with Creatine Monohydrate & NO7 Rage

Active Multivitamin Mineral Formula

- Take two (2) daily: one immediately following first large meal and one following the final meal of the day

SuperOmega-3

- Take one (1) daily if not consuming 2-4 servings of fatty fish weekly

FirstString (or WheySmooth depending on daily calorie allotment)

- Take two (2) scoops 30-45 minutes before workout or use favorite dotFIT® bar for convenience
- Take two (2) scoops 20-30 minutes after post workout AminoBoostXXL dose
- Use anytime throughout the day as a supplement to a meal or by itself mixed with desired ingredients to add protein/calories as needed to meet daily needs.
    - Be sure to ingest ~1 gram of protein per pound of LBM (or weight if not overweight) daily from all sources including food. Ideally, divide protein into 4-5 meals/day along with pre/post shakes (the pre/post combined generally supply 50-80 grams of daily protein goal)

AminoBoostXXL (workout days only)

- Take one and a half (1.5) scoops ~10 minutes before workout (add to NO7Rage if using this product – see below) and may continue to drink during workout
- Take one (1) scoop immediately following workout

Begin Creatine Monohydrate loading at 2nd week of training

Creatine Monohydrate*

- Mix one (1) scoop (5 g) with 4-8 ounces of favorite fluid/shake and take four (4) times daily with a carbohydrate containing meal/drink for first five (5) days. Thereafter take one (1) scoop twice daily to maintain stores. To help maximize creatine uptake, split doses throughout the day with meals/drinks containing carbohydrate and/or protein
- On training days, use one dose before workout and one after with meals/drinks. May mix with your pre/post training formula
- **Dosing by body weight:**
    - Loading phase 0.14 g/LB/d split into four (4) daily intakes of 5 g each, followed by a maintenance phase dose of .04 g/LB/d for the duration of the supplementation period

NO7Rage (workout days only)

One (1) scoop contains 2.5 g CrM and 1 g Beta-Alanine

- Take 1 to 2.5 scoops (depending caffeine sensitivity; start with one (1) and increase to two (2) if not uncomfortably affected by caffeine) approximately 10 minutes before workout (may mix with AminoBoostXXL and continue to consume during workout). See directions on label for weight dosages
    - NO7Rage contains 175 mg of caffeine per scoop. *As a reference: Starbucks Grande-drip coffee contains ~330 mg of caffeine, close to the same amount in two (2) scoops of NO7Rage*

**Programs total daily creatine first 5 days: 20 g/d (plus 2.5-5 g from NO7 on training days). Maintenance phase: workout days = 12.5-15 g; non-workout days-10 g. To maximize uptake, creatine intake should be spread as evenly as possible throughout the day and around the workout as described and ingested with carb and/or protein containing meals or shakes.*

Adult Performance & Size Supplement Plan & Instructions with Creatine Monohydrate and CreatineXXL

Active multivitamin mineral formula

- Take two (2) daily: one (1) immediately following first large meal and one after final meal of the day

SuperOmega-3

- Take one (1) daily if not consuming 2-4 servings of fatty fish weekly

FirstString (or WheySmooth depending on daily calorie allotment)

- Take two (2) scoops 30-45 minutes before workout or use favorite dotFIT® bar for convenience
- Take two (2) scoops 20-30 minutes after post workout AminoBoostXXL dose
- Use anytime throughout the day as a supplement to a meal or by itself mixed with desired ingredients to add protein/calories as needed to meet calorie and protein requirements
    - Be sure to ingest ~1 g of protein per pound of LBM (or weight if not overweight) daily from all sources including foods divided 4-5 times daily along with the pre/post shakes (the pre/post combined generally supplies 50-80 g of the daily requirement)

AminoBoostXXL (workout days only)

- Take one and a half (1.5) scoops approximately 10 minutes before workout (add to NO7Rage if using this product – see below) and may continue to drink during workout
- Take one (1) scoop immediately following workout

Begin Creatine Supplementation at 2nd Week of Program

2nd Week Start Creatine Monohydrate (CrM)*

- Mix one (1) scoop (5 g) with 4-8oz of favorite fluid/shake and take four (4) times daily with a carbohydrate containing meal/drink for first five (5) days
    - On training days, use one dose before workout and one after with meals/drinks. May mix with your pre/post training formula
- After five (5) day loading phase take one (1) scoop daily with post workout shake. On non-training days take one (1) scoop with any meal when not taking CreatineXXL (i.e. use CreatineXXL at different times so total creatine is evenly dispersed throughout the day)

Add CreatineXXL on 6th day of 2nd Week

16 tabs supply 3.2 g of beta-alanine and 6 g of creatine monohydrate

- Workout days take 16 tabs: eight (8) tabs with pre-workout full meal (generally two to three hours pre-workout). If not possible based on early training, take with pre-workout shake. Split the remaining 8 tabs evenly with meals such as four (4) with one meal and four (4) with another
- Non-workout days take 16 tabs evenly split with meals (i.e. 4 tabs with 4 meals) when not taking CrM (i.e. spread entire creatine dosage as evenly as possible throughout the day)

**Programs total daily creatine: Loading phase 20gms/d. Thereafter 11gms/d. To maximize uptake, creatine intake should be spread as evenly as possible throughout the day and around the workout as described and ingested with carb and/or protein containing meals or shakes.*

Adult Super Stack Performance & Size Supplement Plan

Active Multivitamin Mineral Formula

- Take two (2) daily: one (1) immediately following first large meal and one after final meal of the day

SuperOmega-3

- Take one (1) daily if not consuming 2-4 servings of fatty fish weekly

FirstString (or WheySmooth depending on daily calorie allotment)

- Take two (2) scoops 30-45 minutes before workout or use favorite dotFIT® bar for convenience
- Take two (2) scoops 20-30 minutes after post workout AminoBoostXXL dose
- Use anytime throughout the day as a supplement to a meal or by itself mixed with desired ingredients to add protein/calories as needed to meet calorie and protein requirements
    - Be sure to ingest ~1 g of protein per pound of LBM (or weight if not overweight) daily from all sources including foods divided 4-5 times daily along with the pre/post shakes (the pre/post combined generally supplies 50-80 g of the daily requirement)

AminoBoostXXL (workout days only)

- Take one and a half (1.5) scoops approximately 10 minutes before workout (add to NO7Rage if using this product – see below) and may continue to drink during workout
- Take one (1) scoop immediately following workout

Begin Creatine Supplementation at 2nd Week of Program

2nd Week Start Creatine Monohydrate (CrM)*

- Mix one (1) scoop (5 g) with 4-8 ounces of favorite fluid/shake and take four (4) times daily with a carbohydrate containing meal/drink for first five (5) days
    - On training days, use one dose before workout and one after with meals/drinks. May mix with your pre/post training formula
- After five (5) day loading phase take one (1) scoop daily with post workout shake. Non-training days take one (1) scoop with any meal when not taking CreatineXXL (i.e. use CreatineXXL at different times so total creatine is evenly dispersed throughout the day)

Add CreatineXXL on 6th day of 2nd Week

16 tabs supply 3.2 g of beta-alanine and 6 g of creatine monohydrate

- Workout days take 16 tabs: eight (8) tabs with pre-workout full meal (generally two to three hours pre-workout). If not possible based on early training, take with pre-workout shake. Split the remaining eight (8) tabs evenly with meals such as four (4) with one meal and four (4) with another
- Non-workout days take 16 tabs evenly split with meals (i.e. 4X4) when not taking CrM (i.e. spread entire creatine dosage as evenly as possible throughout the day)

Add NO7Rage at 4th week (workout days only)

One (1) scoop contains 2.5 g CrM and 1 g beta-alanine (BA)

- Take one to two and a half (1-2.5) scoops (depending on weight and caffeine sensitivity; start with one scoop and increase to two (2) if not uncomfortably affected by caffeine) approximately 10 minutes before

workout (may mix with AminoBoostXXL and continue to consume during workout). See directions on label for weight dosages

- NO7Rage contains 175 mg of caffeine per scoop. *As a reference: Starbucks Grande-drip coffee contains ~330 mg of caffeine, close to the same amount in two (2) scoops of NO7Rage*

Programs total daily creatine: Loading phase 20 g/d. Thereafter until fourth week 11 g/d. At fourth week on workout days 13.5-16 g/day and 11 g on non-workout days. Total BA intake 5.2 g/day on workout days (two (2) scoops NO7Rage). 3.2gms on non-workout. To maximize uptake, creatine intake should be spread as evenly as possible throughout the day and around the workout as described and ingested with carbohydrates and/or protein.

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