A Review of Creatine and Its Role in Muscle Strength and Balance

by

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Abstract

Creatine (Cr), a nitrogen-based amino acid-derivative, is most well-known in its supplemental powder form, creatine monohydrate, although it is ubiquitous throughout our food supply and within our skeletal muscles and organs. Creatine has recently been tested as a potential therapeutic treatment for disease states such as Alzheimer's, Parkinson's, heart failure, and kidney ischemia. The purpose of this research paper is to provide an overview of recent literature and to expand current understanding of the many roles of this important nutritional compound related to health, disease, and physical activity. Peer-reviewed research papers from the past decade (2007 – 2017) were obtained through an extensive search of the following search engines: Medline, PubMed, ScienceDirect, and SPORTDiscus.

Background

Composition

Creatine (Cr) is a nitrogen-based amino acid-derivative found in the muscle and organ cells of vertebrae (Figure 1). It is a member of the guanidino phosphagen family, which is unique to eukaryotes. Within humans, 95% of creatine is contained in the muscular system, with the remainder dispersed between organs such as the kidneys, heart, and brain. Cr is a key aspect of creatine phosphate, an energy compound necessary for skeletal muscle contraction.

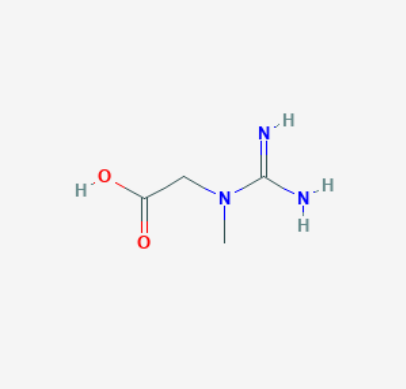


Figure 1: The chemical structure of creatine [1], $C_4H_9N_3O_2$

Creatine also plays roles in acid-base regulation and protein synthesis. This compound is most commonly known today in its supplemental powder form-- creatine monophosphate (CM)-- and taken by recreational and elite athletes alike in order to increase adenosine triphosphate (ATP) production for heightened energy.[2] This increased energy is typically used under anaerobic conditions, high rates of energy transfer, or during times of rapid changes in energy requirement such as weightlifting.

In addition to its noted energy-enhancing properties, creatine may improve post-exercise recovery, thermoregulation, rehabilitation, injury prevention, and concussion and/or spinal cord neuroprotection. Many studies are being done on creatine's applications in health, medicine, and sport. It is evident that Cr contributes to cellular metabolism in at least three distinct ways; as immediate energy; as a spatial energy buffer; and as a metabolic regulator of oxidative phosphorylation. However, there is much potential for creatine to have more functions than originally theorized.[3]

Endogenous Production

Humans synthesize creatine by way of three amino acids; glycine, arginine, and methionine, and two enzymes; l-arginine:glycine amidinotransferase (AGAT) and *N*-guanidinoacetate methyltransferase (GMAT). The membrane carrier, SLC6A8-- also known as CRT1, CT1, CreaT or CRT-- is involved as well. Cr synthesis begins in the kidneys with arginine and glycine reacting to form guanidinoacetate. The methylation of this compound occurs in the liver via S-adenosyl methionine (SAM). Once creatine is synthesized, it is released into the blood. Circulating creatine may enter cells via a Na^+/Cl^- transporter, via the creatine transporter [CRTR], or it may be converted to phosphocreatine by creatine kinase enzymes. Roughly 95% of creatine produced endogenously ends up in skeletal muscle; the remaining five percent is found in organs such as the kidney and brain.[4]

Within these tissues, creatine is found in its free form (Cr) as well as its phosphorylated form, phosphocreatine (PCr). The latter of these two compounds comprises over half of the creatine within a resting muscle. PCr is used in the synthesis of ATP through an anaerobic pathway during high-intensity exercise and requires the presence of an enzyme known as creatine phosphokinase (CPK) or creatine kinase (CK). Phosphocreatine transfers a phosphoryl

group to ADP in order to contract muscles; this transformation from phosphocreatine back to creatine is catalyzed by creatine kinase (Figure 2).[5]

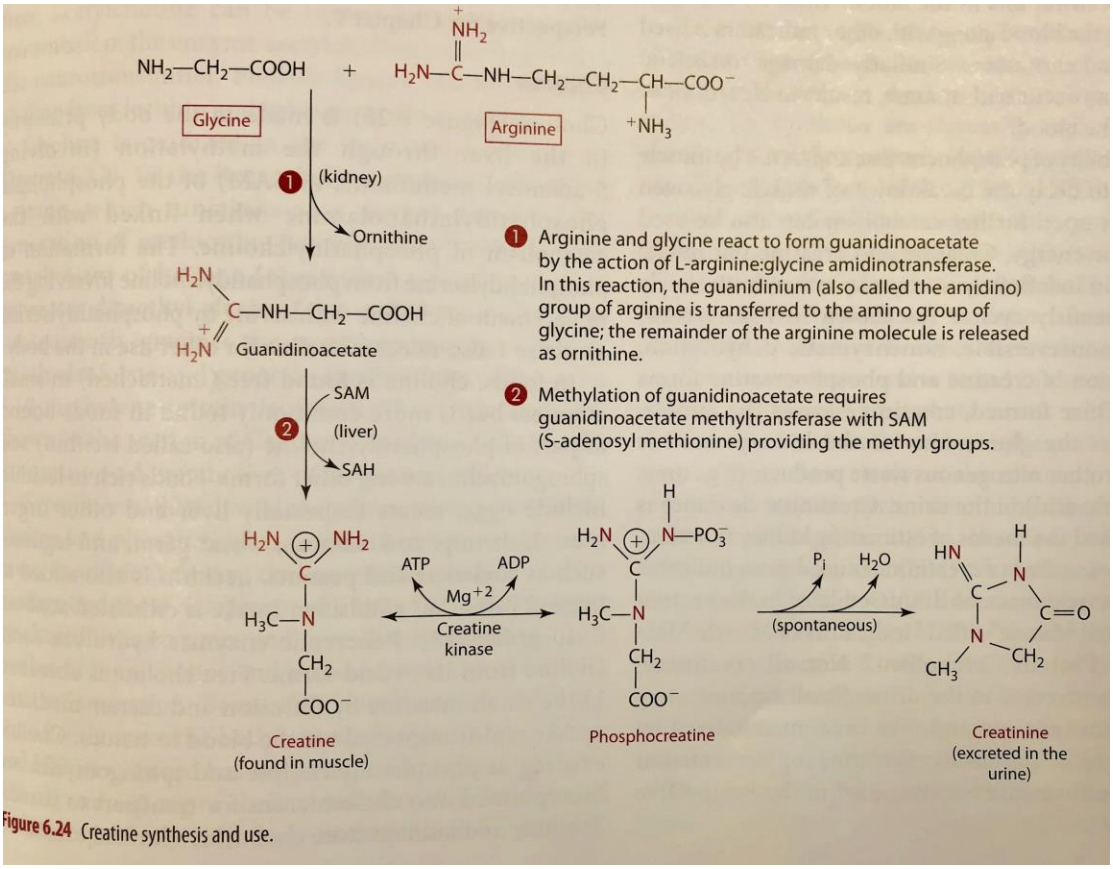


Figure 2: The synthesis of Cr, phosphocreatine, and creatinine [5]

Additionally, AGAT and GMAT are both expressed within the central nervous system (CNS), suggesting that the brain synthesizes its own Cr as well. While SLC6A8 is found within some cells at the blood-brain barrier (BBB), it is absent from astrocytes; this indicates the low permeability of the BBB for creatine. Since the CNS ensures the body gets all of its Cr needs, it is evident that creatine is synthesized to some degree within the brain.

The Cr/PCr/CK system has been shown to be essential in preserving energy levels necessary for the maintenance of membrane potential and ion gradients, calcium homeostasis, neurotransmission, and intracellular signaling systems within the central nervous system. The

Cr/PCr/CK system also plays essential roles in CNS development. Different studies showed that CK isoforms are found highly concentrated in cerebellum choroid plexus and hippocampal granular and pyramidal cells.[6] The hippocampus is important to learning and memory function, linking the theoretical therapeutic use of creatine to Alzheimer's disease. With this correlation in mind, researchers believe the declining creatine pool (comprised of total endogenous PCr levels + endogenous Cr levels) has a moderate effect on whether a person will develop a neurological disorder or not.

The total creatine pool is, on average, 120 grams for a 70-kg individual. Every day, about one to two percent of this pool is broken down into Cr in the skeletal muscle.[7] Due to this constant and cyclical breakdown, it is important to maintain a steady intake of creatine for proper storage and muscular health.

Dietary Sources

For omnivorous humans, dietary intake is responsible for about half of the daily Cr needs.[8] Wild game is considered to be the richest source of creatine; this includes lean red meats such as deer and bison. Fish such as herring, salmon, and tuna also contain high levels of this compound.[1] However, even these prime sources must be consumed in very large quantities to obtain gram quantities of creatine.[9]

Sometimes referred to as a "carninutrient," creatine is only found in meat sources, primarily the aforementioned animals, and to a lesser extent, some dairy products (Figure 3). Vegetarians receive minuscule amounts of dietary creatine[10], while vegans and infants fed on soy-based formulas receive none. Due to this, these populations, specifically formula-fed infants, must synthesize about 90% of their daily requirement.[11] A recent study by Solis *et al*.[10] reported that vegetarians almost always have lower plasma creatine levels when compared to their meat-

eating peers, but creatine levels within brain tissue were comparable to those of omnivores, indicating that dietary creatine intake does not determine the brain creatine concentration. However, in an analysis of muscle creatine, vegetarians showed much lower levels. These findings provide further evidence for the possible synthesis of creatine within the central nervous system.[12]

Food	*Creatine content*	
	g/lb	*g/kg*
Cod	1.4	3.0
Beef	2.0	4.5
Herring	3.0–4.5	6.5–10.0
Milk	0.05	0.1
Pork	2.3	5.0
Salmon	2.0	4.5
Shrimp	Trace	Trace
Tuna	1.8	4.0
Plaice	0.9	2.0
Fruits/vegetables	Trace	Trace

Adapted from Williams MH, Kreider RB, Branch D. Creatine: The Power Supplement (p 15). Human Kinetics, Champaign, IL, 1999

Figure 3: Amounts of creatine in various common foods [13]

Dietary creatine is readily absorbed regardless of the source, although there can be some losses during cooking when high heats are involved. Boiling meat spurs the conversion of creatine to creatinine; for example, boiling chicken breast or stewing beef for 20 minutes retained about 90% of the creatine in the raw meat, whereas more prolonged boiling (roughly one hour) caused a loss of up to 30% of the original creatine. Concerning the method of air-drying to preserve meat or fish, creatine content is reported to remain the same. This retainment is also seen in salted and dry-cured hams.[12]

Intake in the United States

Little is known about the current dietary intake of creatine within the United States.

Quantitative data regarding intake were difficult to find during the writing of this paper. Dietary levels of creatine are not regulated nor listed on Nutrition Facts labels. However, it is common knowledge that people practicing a vegetarian or vegan diet ingest little to no dietary creatine, whereas a meat-eating person would ingest some with every poultry, pork, dairy, or beef product consumed. Lacto-ovo-vegetarians, who consume eggs and dairy, therefore have a higher creatine intake than strict vegans or vegetarians.

Variance Between Age Groups

It makes sense that creatine intake should vary between age groups as well; younger adults, specifically men, tend to eat diets higher in meats than their older counterparts or young children without adult teeth. As one reaches elderly status, the production of stomach acid decreases, tooth loss may occur, and a decline in appetite is typically seen. These factors influence the intake of all foods and especially tougher-to-chew meat products. The prevalence of lactose intolerances and lactose malabsorption are increased in the elderly (sixty-five years of age and older) although the mechanisms responsible are still unclear[14]-- this combination decreases the amount of dairy intake, once again causing a lowered intake of creatine within this population.

Infants consuming breast milk receive much more creatine than their soya-based formula-fed peers. Researchers at Cambridge found that breastfed infants receive about nine percent of the creatine needed in the diet and infants fed cow's milk-based formula receive up to 36% of the necessary Cr. However, infants fed a soya-based infant formula must rely solely on endogenous creatine synthesis. Different formulas also vary in amounts of guanidinoacetate, which plays a factor in how much creatine an infant is able to synthesize (Figure 4).[11] Should an infant receive a formula higher in guanidinoacetate (GAA) and lower in creatine, such as Isomil,

the infant's endogenous synthesis of creatine seemingly "revs up" in order for the child to maintain high enough Cr levels for adequate neurological development.[11]

	Creatine (μM)		Guanidinoacetate (μM)	
	Mean	SD	Mean	SD
Similac (ready-to-use)	114	3	1·1	1·9
Similac (concentrated)	119	7	3·0	4·3
Isomil	13	2	1·9	1·2
Enfalac	334	10	3·7	1·1
Enfamil A +	311	18	3·5	0·4
Lactofree	10	2	ND	ND
Nestlé Good Start	159	5	ND	ND
Nestlé Alsoy 1	11	6	0·3	0·4

Figure 4: Creatine and guanidinoacetate concentrations in various infant formulas (Mean values and standard deviations, n 6 (except n 5 for Nestlé Alsoy 1)) [11]

The amount of intramuscular and intestinal creatine varies between individuals of adult age as well. Once again, those who follow either lacto-ovo-vegetarian or vegan diets have lower levels, and individuals consuming high amounts of fish or other meat have elevated levels.[14] Kerksick *et al*.[15] found that intramuscular ATP levels were roughly 13.5% lower in older non-sedentary males as compared to their younger cohorts. This finding was significantly correlated to age ($r = -0.38$, $p = 0.008$). The older cohort consumed significantly less ($p < 0.05$) dietary protein when compared to the young cohort. However, there was no significant change in levels of PCr, free creatine, or total body creatine. This lack of variance in these intramuscular PCr system markers, suggests older individuals experience mitochondrial dysfunction. Previous observations have indicated age-related reductions in intramuscular ATP concentrations and dietary protein/creatine intake, and this study expands upon that knowledge.

Pregnant Women & Developing Fetuses

During pregnancy, the human body experiences heightened metabolic activity. Due to this,

creatine has been hypothesized to be beneficial to a developing fetus in times of high oxidative stress or feto-placental hypoxia. Dickinson *et al*.[16] noted the difficulty in early predictions of preterm birth/perinatal hypoxia, the sequential narrow window for therapeutic treatment, and the multi-organ dysfunction which is often an outcome, and suggested Cr supplementation within the third trimester of pregnancy. Several animal experiments have shown positive results with regard to the protection of the fetal brain, diaphragm, and kidney against hypoxic insults.[17,18,19] These researchers compare creatine to folate in terms of necessity to prevent infant defects-- a bold claim in the world of nutrition.

Obviously, there are major disadvantages to being born prematurely. The major organ systems have not developed sufficiently to meet the needs of life outside the womb; for this reason, Dickenson *et al*.[16] suggest paying close attention to creatine status of these infants. The heart, lung, and kidneys will require additional support to function, and their incomplete formation puts these organs at risk for ischemic events and mental disabilities. Hypoxia-ischemia at birth occurs in every 4/1000 live term births, with a roughly eight percent mortality rate. Those who survive tend to live with severe health problems due to the irreversible damage to the heart, brain, kidneys, and sometimes lungs. These damages can cause mental and physical disabilities, cerebral palsy, and epilepsy.

The pleiotropic properties of Cr are due to the roles of the PCr system, such as acid-base balance, antioxidant, improved cerebral vascular functions, and stabilization of lipid membranes. These properties are all vital for fetal health during the transition from the womb outward. Within the placenta, the mRNA for CrT is found early in pregnancy and the capacity of maternal-fetal Cr transfer is present from at least 13 weeks of gestation, eliciting the idea that

creatine supplementation during pregnancy could help the fetus develop more rapidly, should a preterm birth occur.[16]

With regard to the mother, little is known about the normal Cr status of pregnant women. In this population, muscle creatine levels might be elevated due to the higher energy needs within the labor process. Cr may be relevant to alleviating preeclampsia; a common syndrome which usually occurs around 20 weeks gestation, with symptoms such as hypertension, maternal end-organ dysfunction, and intrauterine fetal growth restriction. Fetal hypoxia arises during this condition. Thus far, therapeutic interventions for this condition include maternal bed rest, low dose aspirin, or conventional nutrient supplementation. All have shown limited success. Creatine supplementation would allow conservative management and provide the energy needed for the maternal body to recover, as well as the fetal body to continue developing at normal rates.[17]

Creatine as A Sports Supplement

The interest in sport-related creatine supplementation emerged from a paper in 1992 wherein Roger Harris *et al*.[20] demonstrated that five days of a 20-gram dosage of oral creatine monohydrate per day increased total muscle creatine and phosphocreatine by 15–20%. Further research demonstrated similar increases in creatine and phosphocreatine after a month of 3 g/day creatine administration; after a "loading" dose of 20 g Cr/day for 6 days; and after 2 g Cr/day for another month.

The creatine levels in muscle normalize after 5–8 weeks, once supplementation ends. The maximum muscle concentration of total creatine is roughly 160 mmol/kg/dry muscle weight. The World Anti-Doping Agency does not include creatine on its banned supplement list due to the muscle biopsy that would be required to check for Cr loading. The potential for genetic

variations in creatine transport capacity could cause unexplained elevations, which would be unexplainable through muscle biopsy and thus create an unfair advantage.[21]

Most studies report an increase in endogenous creatine pools following supplementation. A positive relationship exists between this elevation and exercise performance; Volek *et al*.[22] observed a significant increase in strength performance after a 12-week supplementation period of 25 g/d Cr for one week, followed by 5 g/d Cr dose for the remainder of the training. This correlation was attributed to an increased regeneration of adenosine triphosphate between training sets, allowing athletes to maintain a higher training intensity.

The knowledge concerning bioavailability of creatine supplements, however, is slim. Several studies examining feces and urine have been unable to find any traces of creatine. While it has been suggested that this supplement is completely absorbed by the intestinal tract, this suggestion has yet to be proven.[23]

Children and Adolescent Supplementation

Little research has been done regarding creatine supplementation or intake within the under age 18 population. Despite this, some young athletes increase their protein intake specifically for creatine levels or supplement with creatine monohydrate. In a report conducted on middle and high school-aged students (all ≤ 18 years old) in Westchester County, New York, 62 of the 1,103 students were using creatine supplements. More research needs to be done about this population; the safety of this supplement has not been examined or established and is therefore not recommended for those under age 18 at all. It must be noted, however, that these data were gathered from a questionnaire and are not representative of all youths in the nation.[24]

Although safety levels have not been set, creatine supplementation may bolster the rate at which phosphates are regenerated during high-intensity exercises. Children's ability to do so is

less than that of an adult. However, this performance can easily be improved through training, so supplementation is not necessary.

Conversely, the International Society of Sports Nutrition suggests that young athletes can consider a creatine supplement but only under certain conditions. These qualifications include the child being past puberty; that he/she is involved in serious competitive training; the athlete is eating a well-balanced caloric adequate diet; he/she as well as the parents approve and understand the truth concerning the effects of creatine supplementation; supplement protocols are supervised by qualified professionals; recommended doses must not be exceeded; and finally, quality supplements are administered.

With all of this, creatine supplementation in young, post-pubertal athletes might not be detrimental. These young adults might see additional benefits to their training outcomes. However, within the everyday child, or those still experiencing puberty or yet still pre-pubescent, it is better to stick to only dietary sources of Cr.[21]

Physiological Roles of Creatine

Skeletal Muscle

Phosphocreatine is described as a "storehouse for high energy phosphate." This compound replenishes adenosine triphosphate (ATP) within contracting muscles via a ceding of a higher phosphate group transfer potential. PCr converts adenosine diphosphate (ADP) to ATP, providing the energy necessary for these muscle contractions. Creatine kinase catalyzes the reaction, with help from free magnesium ions (Mg^{2+}) within the surrounding cytoplasm (Figure 5).[5]

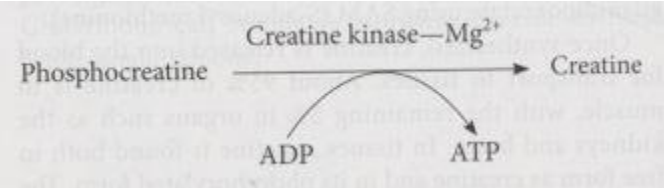


Figure 5: The reaction which converts phosphocreatine to creatine, using the CK enzyme [5]

Due to the reversible nature of this reaction, the body can either utilize PCr to regenerate ATP or to "capture" available cellular energy in the form of adenosine diphosphate. The CK system stabilizes the concentration of ATP at approximately 3–6 mM, which maintains the intracellular ATP/ADP ratio at a very high level. This guarantees efficient ATP use for cellular functions; the energy gained from each hydrolyzed ATP remains at a physiological upper limit. Once a muscle contracts, resynthesis of ATP by the CK system also removes products of ATP hydrolysis, so that the net product of the ATPase enzyme plus the CK reaction is the liberation of inorganic phosphate (Pi) as a metabolic signal. Thus, the CK acts not only as an energy buffer but also as a metabolic regulator.[25]

Over 90% of creatine is taken up into skeletal muscle and found in concentrations up to 130 mmol/kg dry muscle mass.[26] However, some age-associated reductions in this skeletal muscle concentration have been reported, such as within sarcopenia-- the loss of muscle tissue mass as it is related to the natural aging process. This decrease within the creatine pool could be due to age-associated changes in behavior, e.g. reduced physical activity or changed diet or a decreased endogenous maintenance ability.

Fibers within skeletal muscle can be categorized into two types: slow-twitch (Type I) and fast-twitch (Type II). Type I muscle fibers (MFs) are more efficient over long periods of time and are mainly used for endurance exercises-- in other words, they are the aerobic fibers. Type II MFs use anaerobic respiration and are more beneficial during short bursts of speed and energy. This second type also has a greater phosphocreatine content, exhibiting roughly 86 mmol/kg dry muscle vs. Type I's approximate 74 mmol/kg dry muscle. Sarcopenia is typically characterized

by Type II muscle fiber atrophy, which is congruent with the loss of creatine within skeletal muscle over time.[27]

Creatine also provides a protective effect upon markers of stress or activity induced damage in skeletal muscles. In a study focused on triathletes, half of the group was randomized into a placebo (Pl; n = 4) and the other half into a creatine-supplemented group (CrS; n = 4). This latter group received 20 g/d of creatine monohydrate plus 50 g/d of maltodextrin for five days. The Pl group received only the 50 g/d of maltodextrin. The CrS group had decreased plasma activities of creatine kinase and reported a delayed fatigue in addition to lack of muscle soreness. Creatine kinase is considered a biochemical marker of muscle damage, so the decrease of its production following supplementation and a rigorous activity such as a triathlon-- which definitely damages the muscles-- is interesting. Plasma CK activity also marks muscle fiber disruption but has not been shown to be correlated with adverse muscle function following physical exercise. The delayed muscle fatigue noted in the athletes may showcase Cr's involvement in the protection against exercise-induced muscle injury, but more studies must be done.[28]

Skeletal muscle has also been found to become more oxidative with aging-- a decreased reliance on glycolysis has been noted in several studies.[28, 29] Phosphocreatine's availability and usage within skeletal muscles are thought to delay the breakdown of glycogen stores. Creatine and creatine phosphate spontaneously cyclize due to non-reversible, non-enzymatic dehydration, and form creatinine. Creatinine will leave the muscle to pass through the kidneys and is excreted much like other nitrogenous waste. Due to this excretion, urinary creatinine, as a coefficient based on weight or height, can be used to determine kidney function and is used as an indicator of existing muscle mass (approximately 0.3-0.5% of muscle mass by weight is creatinine).

However, due to variations in muscle creatine content, this assessment of nutriture is not always accurate.[5]

While there have been no signs of creatine supplementation enhancing muscle glycogen stores, Hickner *et al*.[28] found positive effects of Cr supplementation with regard to enhancing initial muscle glycogen. Two hours of cycling were done by participants in this study, and the Cr-supplemented group also showed a higher maintenance level of glycogen throughout the exercise. The general sports nutrition consensus is that glycogen depleting exercises should be combined with high carbohydrate and protein diets-- including creatine-- to achieve these heightened muscle glycogen stores. Studies focused on creatine supplements, in their various forms, need to be done in order to solidify these data.

Mitochondrial Dysfunction

Patients with mitochondrial diseases and dysfunctions have been found to have lower levels of total creatine and PCr within their skeletal muscles. These diseases result from mutations which cause defective oxidative phosphorylation. This defected process leads to an increased reliance on anaerobic energy sources and increased plasma lactate concentrations. The PCr system, in junction with glycolysis and glycogenolysis, can be used to supply ATP; however, an increase in the latter processes results in elevated lactate. Rodriguez *et al*.[30] looked into the connection between these processes and mitochondrial dysfunction. Creatine monohydrate therapy was used to enhance the PCr system within patients with mitochondrial diseases. An increase in urinary creatine:creatinine ratios and lowered plasma lactate levels immediately following supplementation was found, suggesting creatine monohydrate may provide the body an alternative anaerobic source of energy.

Supplementation of creatine has been used as a treatment in muscle dystrophies,

cytopathies, inflammatory myopathies, and peripheral neuropathy disorders for several years. A recent randomized controlled trial found this supplementation can enhance muscle function in patients with dystrophies who were clinically weak due to pharmacological treatment.[31] Kley *et al*.[32] concluded that Cr supplementation promotes muscle strength and lean mass in patients experiencing these muscular dystrophies.

Brain Tissue

The brain uses roughly 20% of the body's energy production, due to high ATP 'costs' of transmembrane ionic gradients. The creatine-phosphocreatine cycle has been hypothesized to aid intracellular energy routing in the brain. Approximately 43% of the cells in the central nervous system possess proteins enabling creatine synthesis and transport. In mature brains, the blood brain barrier is only slightly permeable to physiological concentrations of creatine as a result of a low expression of SLC6A8. In contrast, within developing brains of young children, SLC6A8 is highly expressed.[4]

Despite the discrepancy between SLC6A8 levels, creatine signal from the brain has been reported to grow stronger with age, suggesting that brain bioenergetics capacity increases as well. An increased intake of creatine as one ages could improve overall brain function and specifically positively affect motor control and balance.[33] More studies concerning this must be done in order to have a resounding conclusion.

Interestingly, creatine concentrations in the brain are typically higher than Cr levels in plasma; the difference is roughly 6-12 mmol:40μmol. This supports the hypothesis of active accumulation of brain creatine. Despite this, transfer of this compound across the blood-brain and blood-CSF barriers seems limited. Some cells within brain tissue have been shown to synthesize creatine; these contain enzymes AGAT and GMAT. The latter is absent in many

neurons, adding to the convention that glial cells could be the producers of creatine, allowing neurons to accumulate Cr via SLC6A8.[34]

Cr has also been suggested as an essential CNS osmolyte. Astrocytes placed in hyperosmotic shock increase their Cr uptake, suggesting that creatine works as a compensatory osmolyte in the correct environment. Ammonium-exposed microcapillary endothelial cells (MCEC) *in vitro* also increase their Cr uptake, suggesting that cells making up the blood-brain-barrier behave differently during swelling. Cr was also proposed as an appetite and weight regulator, by acting on specific hypothalamic nuclei.[35] In addition, Joncquel-Chevalier Curt *et al*.[4] proposed that creatine is a neurotransmitter in the CNS which might modulate GABAergic and/or glutamatergic neurons. The relationship between creatine intake and these neurons, as well as what roles creatine might or might not play, still remain unclear.

Primary Creatine Deficiency Disorders

Inborn errors caused by mutations in either amidinotransferase or *N*-guanidinoacetate methyltransferase, or within the creatine transporter SLC6A8, have been reported in children. These patients exhibit neurological impairments such as epilepsy and speech delay, as well as an almost complete absence of creatine from the brain. Following therapeutic creatine treatments, this population showed a slower restoration of brain creatine levels and some symptomatic improvements. No reversal of the pathology was seen. Children with defects involving SLC6A8 saw no effects.[35]

The studies of these children have revealed that creatine plays a more significant role in brain development than previously thought. Due to this, two children-- one with AGAT deficiency, and one with GMAT deficiency-- were treated with creatine pre-symptomatically; this was possible due to each child having an older sibling who presented with the same disorder,

and the chosen siblings had been previously tested for similar deficiencies. In each of these two cases, symptoms were prevented and normal developmental milestones were reached. More research must be done in order to clearly define the role of creatine within child brain development, but it is clear that this compound is vital in this process.[35]

Neurodegenerative Diseases

Studies focused on both animal and cellular models have shown a positive correlation between creatine ingestion and slowed progression of neurodegenerative diseases. These diseases include Alzheimer's, Huntington's, Parkinson's and amyotrophic lateral sclerosis (ALS). All share attributes such as low brain Cr content, high oxidative stress, and mitochondrial dysfunction. Andres *et al*.[36] found a positive correlation between an alleviation of these symptoms and the administration of a creatine supplement. This correlation has been attributed to improved cellular bioenergetics within an expanded phosphocreatine pool, creating a neuroprotective effect.

Due to these neuroprotective effects, creatine is currently being investigated as a potential treatment for Parkinson's disease. There is also evidence that a higher Cr dietary intake/higher supplementation may slow age-related decreases in muscle mass, bone mineral density, and muscle strength. This could theoretically have a number of beneficial effects for myopathy patients, such as increased muscle mass, strength, and endurance capacity.[37, 38] Should the findings be significant, Parkinson's patients might regularly receive prescriptions of Cr to aid in symptomatic relief from their myopathy.

Strokes

During a stroke, the loss of brain function is due to a lack of blood flow to the brain, thus creating an oxygen/glucose deficiency within these cells. The Cr/PCr system does not require O_2

or glucose to function and can regenerate ATP for a limited time during these circumstances. This has been hypothesized to explain the momentary delay between a stroke occurring in the brain and the onset of symptoms.[39] Prass *et al*.[40] examined mice exposed to transient focal cerebral ischemia, which were in absence of notable changes in brain Cr, PCr, and ATP levels. This observation supports the non-energy related effect Cr potentially has on brain vasodilatory responses.

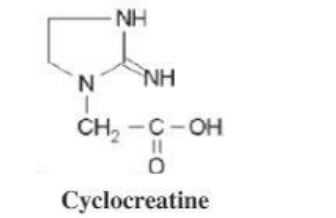
Adcock *et al*.[41] subjected neonatal rates to unilateral common carotid artery ligation followed by 100 minutes of hypoxia (8% O_2). The researchers were able to show that rats which had previously received Cr supplementation had a significant reduction (25%) in edematous brain tissue volume compared to controls.

In a study by Perasso *et al*.,[42] creatine was given as either a pretreatment (0.25 microliters/hour of a 50 mM Cr solution for 5 days prior to ischemia and for a week following) or immediately after ischemia (the same rate, beginning 30 minutes post-incident and continuing for seven days). Cr was shown to provide significant protections when administered before ischemia on all aforementioned parameters.

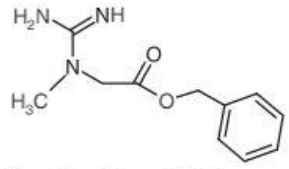
A limitation of pure creatine as a therapeutic method post-ischemic events is its lack of complete permeability across the blood-brain barrier. Adcock *et al*.[41] attempted to use Cr-derived compounds rather than pure creatine which they theorized would reproduce creatine's neuroprotective effects while reaching the affected area of the brain more rapidly. Derivatives included cyclocreatine, creatine-benzyl-ester, and phosphocreatine-Mg-complex acetate (PCr-Mg-CPLX) (Figure 6)[41]. The latter was the only derivative to show reproducible positive results; that is, when PCr-Mg-CPLX was injected into mice subjected to middle cerebral arterial occlusion, there was a decrease of the volume of damaged tissue and of ischemia-induced

behavioral alterations.

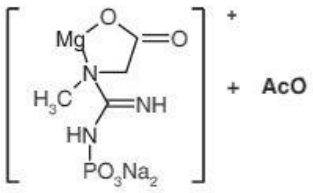
The obvious limitation here is that brain tissue seems to require pre-treatment with creatine; it may only be applicable to clinical situations wherein brain ischemia is predicted, such as patients considered high-risk cardiac surgery or endovascular brain procedures (intracranial stenting or embolization of arteriovenous malformations). Research is lacking with regard to Cr treatment post-strokes. Methods to improve Cr/PCr delivery across the BBB and into the extracellular space should be devised.



Cyclocreatine



Creatine-Benzyl-Ester



Phosphocreatine-Mg-complex acetate

Figure 6: Cr-derivatives used by Adcock et al. in an attempt to cross the BBB [41]

General Brain Myopathies

A complete lack of creatine in the central nervous system can be caused by a deficiency of glycine amidinotransferase and guanidinoacetate methyltransferase. This leads to creatine

deficiency syndromes. Brain creatine deficiency resulting from dysfunctioning CreaT (the membrane carrier, SLC6A8) has been shown to be unresponsive to oral creatine supplementation. Other forms of myopathy have shown conflicting results depending on the type of myopathy and Cr transport systems disorders.[42]

Cr has also been found to possess anti-apoptotic and direct antioxidative pleiotropic effects.[39] With apoptosis decreased, cells could replicate as necessary. With some pleiotropic genes expressing antioxidative properties, they can function as normal despite the possible oxidative damage. This has been associated with a marked improvement in cognitive performance in the elderly [43] and alleviated mental fatigue due to sleep deprivation.[44]

Seizures

Though creatine is most known for its ergogenic properties, evidence has shown that Cr also has anticonvulsant properties related to seizures. Free creatine, as well as phosphocreatine, increased latency:population spike disappearance during anoxia and anoxic depolarization. Anoxic "bursting" in hippocampal sites was also found to be decreased when creatine supplements were given.[45] It has been proposed that at least part of these properties are due to creatine's antioxidant effects. Oxidative stress has been known to propagate seizures in several types of epilepsy, but little research regarding this link is available. The aforementioned range of situations in which Cr has shown neuroprotective properties provides good reason to establish creatine supplementation as a preventative therapy for epilepsy and other neurodegenerative diseases (Figure 7).[46]

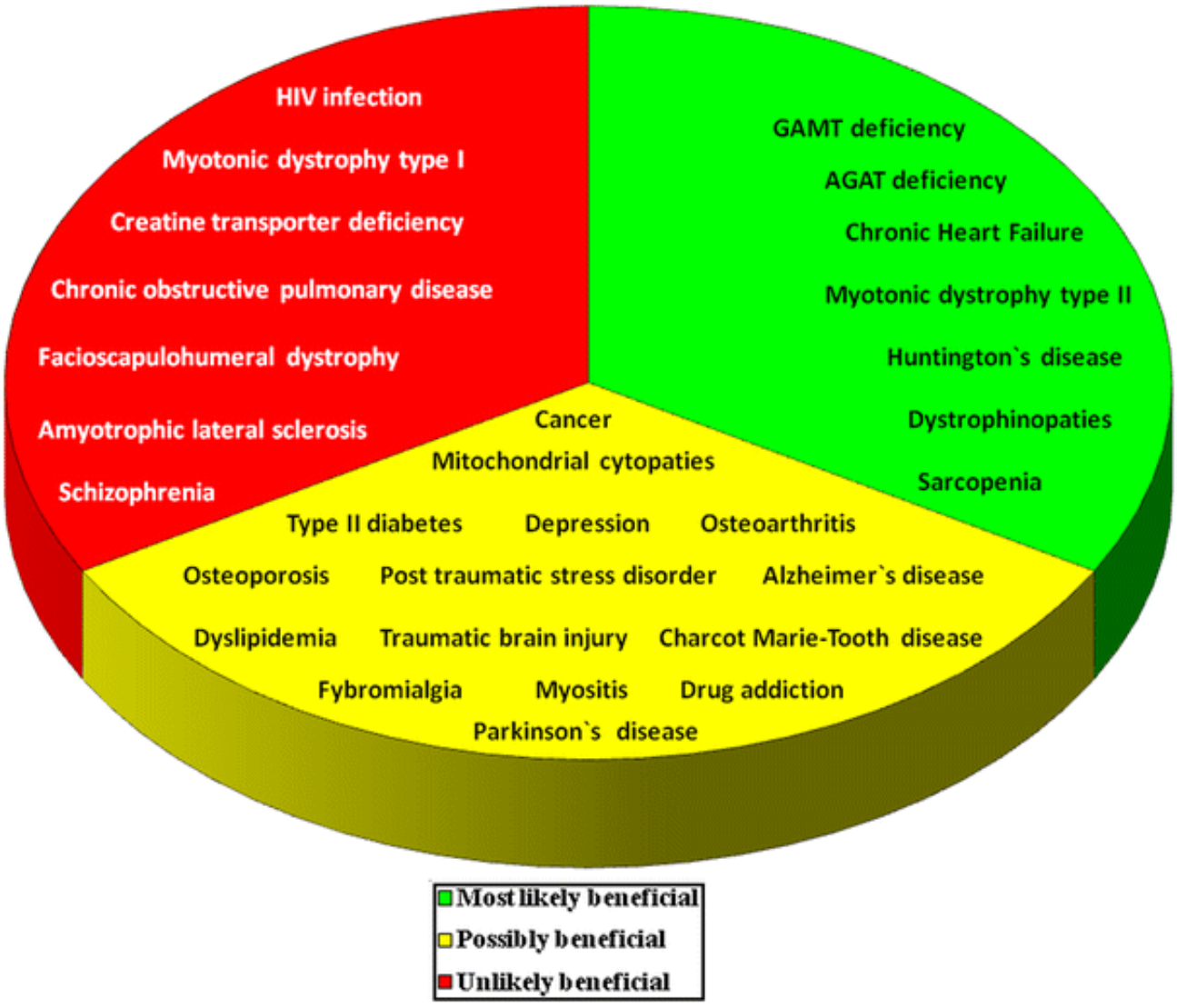


Figure 7: Diseases states in which creatine supplementation has been used as a treatment and how beneficial it appears to be from clinical trial data [46]

Heart

Within the heart, the creatine kinase system acts as an energy buffer. The phosphocreatine level falls when the demand for energy outweighs the energy supply; this increases free ADP levels as well. With this higher amount of free ADP, many intracellular enzymes are inhibited causing the heart's contraction to fail.

Impaired oxidative phosphorylation is also problematic when it comes to the heart's function. An insufficient ATP supply to the cardiac myocytes does not allow the heart to beat as required, and creatine enzymes- specifically creatine kinase- fail to work.[47]

In the cardiac muscles, CK is made up of two subunits--M and B. When the heart is damaged, an enzyme leakage occurs; this spills out, elevating CK-MB within the blood.[5] It is this elevation of CK-MB levels in the blood that is used to diagnose heart attacks. ATP levels within heart tissue remain normal, at roughly 10 mmol per liter, until the advanced stages of heart failure (HF). These decrease by 30 to 40% within advanced HF. However, phosphocreatine and total creatine levels decrease at earlier stages and have been found to decrease by 70%. This is due to changes in the creatine kinase system.[47]

Creatine has also been linked to stabilizing bioenergetics within cardiac muscles during times of decreased blood flow and oxygen to the heart-- otherwise known as ischemic events. Due to this stabilizing effect, there is growing interest in the role of Cr and PCr within normal heart function as well as in potentially reducing tachycardia events. Phosphocreatine supplementation has been shown by Balestrino *et al*.[48] to treat ischemia and improve overall heart function, with moderate success. Regular creatine supplementation might protect the heart during these events, leading us to believe Cr intake could be increased in patients at risk for ischemia/stroke as a preemptive measure.

It has also been hypothesized that there is a causal relationship between reduced ATP-CK metabolism and contractile dysfunction in total heart failure. In mice with an overexpression of the myofibrillar isoform of CK (CK-M), increased ATP flux through CK was seen *ex vivo* and *in vivo*, but within normal mice there was no altered contractile function. At baseline and during adrenergic stimulation, the CK-M mice experienced higher levels compared to their control

group counterparts. The CK-M mice also saw increased survival following surgery-induced heart failure; once this overexpressed isoform was withdrawn, post-HF there was a significant decrease in contractile function. This study concluded that failing hearts are starved for energy, specifically in the forms of CK and ATP. Creatine kinase was also noted as a potential therapeutic agent for prevention and treatment of HF.[49]

Intestinal

Rather surprisingly, high concentrations of CK have been found in a variety of intestinal epithelial cells that are not known to have high energy requirements. These cells may need energetic support for maintaining cell division rates or for reabsorption or secretion activities.[12]

Intestinal epithelial cells are held together by tight junctions in the apical junctional complex. These structures are in close contact with filaments of the cytoskeleton, and ATP hydrolysis is involved in their maintenance. Disruption of the barrier function of the junctions occurs during inflammatory states when intestinal cells are exposed to a hypoxic environment. Hypoxia-inducible transcription factors (HIFs) are activated in hypoxic situations, such as inflammatory bowel syndrome (IBS). The upregulation of these genes and, consequently, the inflammatory response has been proven to be diminished following creatine supplementation in mouse colitis models. Since chronic inflammation in this region is a major risk factor for colitis-associated colon cancer, an increased Cr intake might be a therapeutic measure to promote epithelial restitution.[11]

The lower GI tract experiences frequent changes in oxygen tension, especially during times of inflammation. CK has been notedly expressed in hypoxia-inducible transcription factor (HIF)-dependent manner within an animal colitis model; supplementation with dietary Cr alleviated the severity of the disease and the inflammatory response.[50] This physiological

response confirms that HIF-CK has a role within epithelial homeostasis which keeps the mucosal barrier intake and functioning. Interestingly, patients with chronic kidney disease (CKD) have a tendency to express intestinal inflammatory bowel disease as well-- should the results of Glover *et al*.[50] be confirmed in humans, these findings may be used in clinical trials to relieve these patients of the noted comorbidity.

Renal

Creatine supplementation on renal function has been heavily studied since the supplement was once thought to have been detrimental. Some regulatory agencies, such as the French Agency of Medical Security for Food (AFSSA) and the Brazilian National Agency for Sanitary Vigilance, have restricted the sale of Cr-based supplements. AFSSA published a report in which it detailed creatine as having a "potential carcinogenic risk." The agency quotes epidemiologic studies that showed creatine causing "digestive, muscular and cardiovascular problems." The Brazilian Agency is of the same opinion.[51] However, the debate remains; evidence on the negative effects of Cr on the kidneys has not been solidified.[52]

Several longitudinal studies have shown that short-, medium-, and long-term Cr supplementation does not affect kidney function in otherwise healthy humans.[53,54] One such study found serum creatinine and Cystatin C levels decreased over a three-month supplementation period. These data indicate that Cr supplementation does not provoke renal dysfunction.[29]

A study by Sale *et al*.[55] showed that short-term (1-10 days) and high-dose Cr supplementation (roughly 20 g/day) increased production of urinary methylamine (a derivative of ammonia) and formaldehyde. These compounds are typically associated with nephropathy and are formed as a result of the conversion of Cr to sarcosine, an amino acid. The lower and more

frequent doses of creatine were shown to reduce the formation of methylamine. Based on these data, it would be recommended that supplementation is taken evenly throughout the day to prevent accumulation of these agents.

Interestingly, studies have recently investigated the protective effects of creatine within dialysis patients. The CK/PCr-system is incorporated in kidney functions; skeletal and cardiac muscles of dialysis patients with CKD have been found to be depleted of Cr in parallel with dialysis duration. Cellular damage in CKD patients leads to deterioration of skeletal muscle, neurological function, and poor quality of life. To counteract this depletion and prevent these side effects, CKD patients are thought to be candidates for Cr supplementation- after all, there have been documented improvements within the musculoskeletal system, brain, and PNS as people increase their Cr intake.[56]

Researchers proposed this supplementation along with an intradialytic route of administration; a small amount (1-10 mM) of Cr would be added to the dialysis solution to enter the patient's circulation during dialysis. Creatine would be actively transported from the bloodstream to the target cells within the kidney's proximal tubules. Due to the method of administration, only as much Cr would be taken up by the body as is needed, therefore avoiding any negative side effects.[55]

Creatine and Patients with Urea Synthesis Disorders

Patients with inborn errors of urea synthesis are typically dependent on *de novo* synthesis for creatine. Due to their urea synthesis disorder (USD), these patients have low protein diets, and, consequently, relatively little creatine intake as well as endogenous levels. One exception to these USDs is arginase deficiency.

Arginase is the final enzyme of the urea cycle and converts arginine to ornithine. This disorder is typically accompanied by hyperargininemia- in most other USDs, hypoargininemia is seen. This is due to arginine's role as an essential amino acid within these patients. Patients with arginase deficiency have enhanced production of guanidinoacetate and therefore elevated creatine synthesis capabilities.[52]

If left untreated, arginase deficiency results in neurological features such as development regression. In addition, increased levels of various guanidino compounds are seen in plasma and tissues, suggesting arginine metabolism increases through a variety of minor pathways. Creatine is one such of these elevated compounds. The mechanism to explain this seems to be straightforward; elevated arginine results in higher amounts of guanidinoacetate produced by the kidney as well as other AGAT containing tissues. Creatine synthesis by the liver typically operates below maximum at circulating GAA levels and responds to increased concentrations of guanidinoacetate by maximizing Cr synthesis.[52, 53]

It has been suggested that brain levels of creatine may be lowered in patients suffering from urea synthesis disorders-- except for arginase deficiency. The presence or absence of a lower than normal level of brain creatine in patients with urea synthesis disorders is unresolved, and inconsistent results may be attributed to heterogeneity within these disease states, differences in the degree of supplementation, and the inherent problems researchers experience when measuring creatine within this area.[52]

Ischemic Kidney Events

The protective effects of Cr and PCr against ischemic incidents with relation to the heart and brain are well noted; these effects might also extend to the kidney. The inner medulla of the kidney typically functions at very low oxygen levels. The kidney's usage of oxygen is associated

with paracellular sodium resorption via the tubular epithelial cells, facilitated by the Na+/K+ ATPase. Regions within the kidney can become ischemic under chronic conditions which cause energy deficits.

Some researchers have theorized that an increase in dietary Cr intake or supplementation will aid in maintaining proper kidney mitochondrial levels as well as alleviating the symptoms of an ischemic kidney, similar to reactions of ischemic events within cardiac muscles. Human studies have shown that Cr supplementation improved the reactivity of systemic endothelial-dependent microvasculature and increased the skin's capillary density. This is highly relevant for dialysis patients and those experiencing CKD. Since failing kidneys would receive benefits, in addition to other energy-deprived organs (skin, cardiac muscle, brain), the comorbidities and risk factors for mortality in patients with ischemic kidneys could potentially be avoided with Cr and/or PCr supplementation.[53]

Antioxidant

Creatine exhibits antioxidant activity through either direct interaction with oxidant species or metabolic action conferring antioxidant protection. In muscle, Cr is readily available to free radicals generated during physical exercise. This availability of mitochondrial kinases creates an ADP:ATP ratio favorable for the respiratory chain to function optimally.[4] By preventing stasis in the electron transfer chain, mitochondrial creatine kinases (MtCK) reduce the generation of oxidant species through a MtCK-dependent ADP recycling activity during exposure to high glucose conditions (Figure 8)[56].

Cr has also been found to decrease the production of superoxide by preventing the creation of high mitochondrial membrane potentials. Part of the antioxidant protection conveyed by creatine may result from either promoting a rise or preventing a drop in cellular antioxidant

defenses.[34] Some studies indicate that Cr may promote oxidative stress and lower antioxidant status of healthy athletes.[37] Anecdotal reports from athletes concerning muscle cramp and gastrointestinal complaints have surfaced, particularly in a report by Kim *et al*.[38] This oxidative stress is considered one of the most important factors contributing to muscle fatigue and damage during exercise.

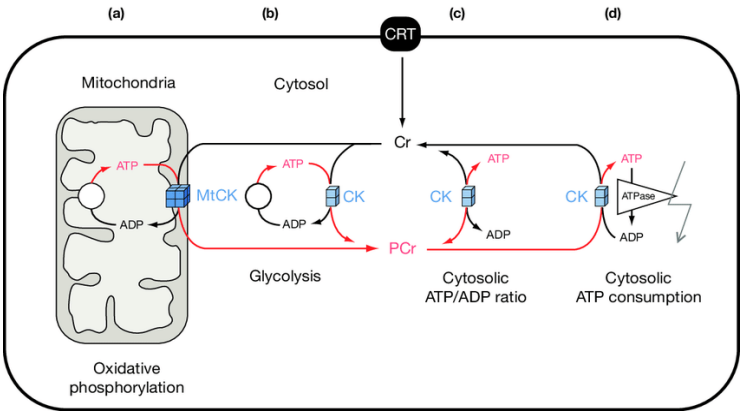


Figure 8: The CK/PCr system for temporal and spatial energy buffering in cells.[56]

Cr has been reported to exert a direct antioxidant activity in cells exhibiting acute free radical damage and specifically protects mtDNA and RNA from oxidative damage. While the antioxidant effect exerted by Cr may be lower than other antioxidants, it is ubiquitous in many cells and is therefore described to be ‘‘physiologically on-board.” Furthermore, PCr appears to be capable of stabilizing cellular membranes due to electrostatic interactions with phospholipids.[37]

Additionally, creatine provides antioxidant effects indirectly. The reduced production of free radical oxygen species by mitochondria occurs when Cr stimulates mitochondrial respiration, via the CK isoform. The creatine kinase isoforms allow for a high-energy phosphate shuttle system in which mitochondrial ATP is immediately used. This process has been seen in skeletal and cardiac muscles, as well as muscle fibers. Due to the high number of mitochondria present in the kidneys, it is assumed that Cr also stimulates the functioning of these as well,

leading to a reduction in oxidative damage and inflammation in the kidneys.[54]

Relationship Between Creatine And Exercise/Movement

Range of Motion

Within a study conducted in 2010 by Sculthorpe *et al*.,[57]it was shown that a five-day loading period of 25 grams Cr/day, followed by another three days of 5g Cr/day negatively influenced ankle dorsiflexion and shoulder abduction in young men. Extension range of movement (ROM) was also negatively affected. Two main hypotheses developed from these findings; 1) Creatine supplementation could increase intracellular water content, thus worsening muscle stiffness and increasing resistance to stretch; 2) Neural outflow from muscle spindles is negatively affected due to increase muscle cell volume.

The researchers noted that the active ROM measures were done immediately following the loading phase, and the reduced ROM was not seen until after several weeks of the maintenance phase.[57] However, Hile *et al*.[58] observed higher compartmental pressure within the anterior lower leg (ACP) and a reduced ROM for which creatine may also have been responsible. These researchers used a 21.6 g/d dosage of creatine monohydrate or a placebo for seven days. On the final day, participants (n = 11) performed two hours of submaximal exercise, switching between walking and cycling every thirty minutes, followed by an 80-minute heat tolerance test. ACP levels did not return to normal until 28 days post-supplementation, indicating that creatine has a lasting effect on ROM and the interior pressure which affects the movements possible.

Aerobic Exercise

Branch *et al*.[59] noted that during endurance activities longer than 150 seconds, muscles primarily rely on oxidative phosphorylation for energy. The researchers expanded on this observation and found the potential for creatine supplementation on aerobic exercises (i.e.

swimming, sprint-running, skating) decreases inversely with the time span increasing past 150 seconds. It has been speculated that the increased body mass following creatine supplementation may be ergolytic for these activities. However, the authors suggest this supplementation may change substrate utilization during this aerobic activity-- leading to an increase in overall steady state endurance performance.

Not all studies have been conclusive on the benefits of creatine supplementation within endurance performance. Graef *et al.*[60] looked at the combination of four weeks of Cr-citrate supplementation, high-intensity interval training, and how these affect cardiorespiratory fitness. The ventilatory threshold-- the point at which ventilation starts to increase at a faster rate than VO_2-- increased within the Cr-supplemented group, but there were no significant differences between the placebo and supplement groups with regard to O_2 consumption. Subsequently, the authors concluded there was no interaction and no main effect for Cr within these aerobic exercises.

During a six-week period of 2 grams Creatine Monohydrate/day for female swimmers, Thompson *et al.*[61] reported no change in aerobic or anaerobic endurance performance. It could be possible that the benefits of creatine supplementation on endurance performance are more related to effects of anaerobic threshold raising, but more studies must be done to conclude this.

Resistance

A comprehensive summary of data concerning creatine supplementation and its effects on athletic performance (up to 2007), published by the International Society of Sports Nutrition suggested the anabolic performance enhancing properties may be due to satellite cell proliferation, myogenic transcription factors, and signaling from insulin-like growth factor-1 (IGF-1).[62]

Burke *et al*.[63] also examined this increased of IGF-1; the effects of a two-month long resistance training program, combined with seven days of creatine loading (0.25 g/kg lean body mass), followed by a 49-day maintenance period of 0.06 g/kg LBM, were examined in a group of co-ed participants (n = 42). Members ranged from vegetarian to non-vegetarian, and novice athletes to thoroughly resistance trained.

The creatine supplemented groups were found to have produced greater amounts of IGF-1 and gained an average of 1.6 kg LBM vs. the non-creatine group. In addition, vegetarians within the supplement group experienced the greatest increase of LBM. The IGF-1 levels were similar within the vegetarians and non-vegetarians.[63]

Saremi *et al*.[64] reported a change in the aforementioned myogenic transcription factors when creatine supplementation was combined with resistance training in young, healthy males. Serum levels of myostatin, a muscle growth inhibitor, were decreased in the supplement group. This supports other studies showing that creatine supplementation amplifies performance within resistance training, with respect to exercise duration and muscle hypertrophy.

The beneficial effects of Cr supplementation on resistance training are obviously a consistent finding and could be contributed to increased training loads following increased pre-exercise PCr within muscle and a higher rate of PCr synthesis. However, these improvements in performance are not limited to longer-term supplementation (>2 weeks). Within two five-day long studies, increased deadlift volume in trained powerlifters and increased maximal squat strength was seen while loading at 20-25 grams Cr/day.[31]

Gualano *et al*.[65] investigated the efficacy of creatine supplementation—associated or not with resistance training—in physically inactive older women (> 60 y.o.) who presented with diagnoses of osteopenia or osteoporosis. Within a 24-week double-blind, randomized, placebo-

controlled trial, subjects were randomly assigned to four groups (n = 15 for each); 1. placebo supplementation (PL); 2. creatine supplementation (CR); 3. placebo supplementation with resistance training (PL+RT); or 4. Creatine supplementation combined with resistance training (CR+RT). The creatine supplemented groups received 20 g/day of creatine monohydrate for five days followed by single daily doses of 5 g for the following 23 weeks. The PL and PL+RT groups received the same amount of dextrose. Resistance training included leg press, leg extension, squat, seated row, bench press, lat pulldown, and sit-ups. After the intervention, the increased repetitions completed per training session were significantly greater in the CR+RT group than in the PL and the CR groups ($p = 0.002$, $p = 0.002$). The CR+RT group also had superior gains in the 1-RM bench press (Pre: 33.9 ± 5.6, Post: 36.5 ± 7.1 kg, +10%) when compared with other groups, in addition to greater lean body mass accumulation. Interestingly, the number of subjects considered sarcopenic at baseline decreased in the CR groups (n = −3) in comparison with the placebo groups (n = + 2). Blood parameters, including creatinine and CK, did not change.[65]

Balance

Johannsmeyer *et al*.[66] assessed balance by recording the average time participants (n = 31) took to tandem walk backwards (i.e. toe to heel) for 6 meters on a 10 cm-wide board raised 4 cm off the ground, in addition to the number of errors (i.e. number of times the participant stepped off the walking board). Participants performed 1 practice and 2 recorded test trials. Participants were split into 2 supplementation groups; Creatine (n = 14; 7 F, 7 M; 58.0±3.0yrs, 0.1g/kg/day of creatine+0.1g/kg/day of maltodextrin) or Placebo (n = 17; 7 F, 10 M; 57.6±5.0yrs, 0.2g/kg/day of maltodextrin). The number of errors ($p = 0.042$, $\eta 2 = 0.15$) and time taken to finish the balance board test ($p < 0.001$, $\eta 2 = 0.70$) were both significant. Both groups

exhibited improvement over time but the magnitude of change was greater in the PL group (pre: 32.8 ± 12.7 s, post: 22.7 ± 10.9 s) compared to the CR group (pre: 28.3 ± 9.0 s, post: 22.8 ± 9.0 s).

Functionality tests	CR group				PLA group			
	Pre	Post	%	*p*-Value	Pre	Post	%	*p*-Value
Balance time (sec)	28.3 ± 9.0	22.8 ± 9.0	19.4	0.002	32.8 ± 12.7	22.7 ± 10.9*	30.8	< 0.001
Balance errors (steps off the board)	2.3 ± 2.1	1.9 ± 1.8	17.4	0.317	2.1 ± 3.2	1.4 ± 2.6	33.3	0.037
Handgrip strength (kg)	40.1 ± 11.9	41.0 ± 12.8	2.2	0.054	40.0 ± 10.6	41.4 ± 11.1	3.5	0.058
80 m walking time (sec)	38.2 ± 4.6	37.1 ± 4.3	2.9	0.045	36.2 ± 5.7	33.9 ± 6.6	6.4	0.001

Values are mean ± standard deviation. % = percent change over time.

Figure 9: Functionality tests before and after 12 weeks of supplementation and high-low resistance training [66]

Analysis of Studies Used

Trends

Within the earlier studies (2007 to 2012), most advised that creatine was used rather sparingly due to lack of knowledge of how urinary and kidney functions would be affected by continual use. Later studies (2012 to present) generally state that there does not seem to be any sort of negative affect from Cr usage on the majority of organs. Usage effects on kidney function still seem to be debatable, however, all of the studies agree that practicing vegetarians and vegans might want to consider taking supplemental creatine, due to the absence of it from their diet.

Comparison Across Studies

Methodologies

Many studies mentioned within this paper examined the creatine:creatinine ratio. This ratio is typically measured due to creatinine's pathway through the glomerulus of the kidneys and its excretion within urea, ammonia, uric acid, and urine, in addition to how it affects the glomerular filtration rate (GFR). Creatinine is also used as a measure of kidney function via GFR and as an indicator of existing muscle mass.

Urinary creatinine excretion reflects about 1.7% of the total creatine pool per day, which was common baseline quantity used within these studies. Total creatine pool size (Endogenous PCr levels + Endogenous Cr levels) was measured in all of the studies with exercising participants and was meant to track how much of this Cr would be broken down in the skeletal muscle. In studies using on non-exercising participants, the creatine pool size was used to estimate the storage of creatine.

Free creatine, surprisingly, was not commonly studied. The dietary intake of creatine sources was only noted in terms of whether participants were practicing vegetarians/vegans or not. Data on the amount of creatine ingested in a typical day was not collected, perhaps due to the difficulty of quantifying Cr in all of the sources consumed within a day for non-vegan populations. More data needs to be collected and averaged on the amount of creatine within omnivorous diets.

Groups Studied

Within groups of participants who were considered moderate intensity to vigorous intensity exercisers, as well as trained athletes, the effects of the supplemental form of creatine monohydrate were the main focus. It would be interesting to see studies performed using similar

groups with regard to the effects of dietary, not supplemental, creatine on physical performance. Though capturing these data is not the simplest of tasks, it would provide invaluable knowledge to variance within groups and their creatine levels.

All of the studies with human participants pointedly note when they are examining non-athletes vs. athletes, to be transparent of variance within skeletal muscle Cr composition. It should also be noted that the majority of studies focus on creatine supplementation and endogenous production only in the younger populations, i.e. less than 50 years of age. This is due to the prevalence of Cr within the exercising/competing athlete communities which are typically comprised of younger adults. In the present search conducted, some studies were found that examined creatine in older populations (> 50 years old), however, most of these studies examined the combined results of creatine and exercise within this age group. It is difficult to separate the effects of creatine ingestion and benefits of exercising in elderly populations. A study focusing on creatine levels within exercising and non-exercising older participants, performed over a longer period of time, might provide better insight with regard to the benefits of exercise versus creatine in this age group.

Conclusion

The discussion on creatine is not over yet; much research still needs to be done. While we are aware of discrepancies between dietary habits, athletes vs. non-athletes, and some clinical uses, creatine could have a plethora of uses that have yet to be discovered. For instance, there could be a variance of Cr skeletal muscle amounts between those of healthy BMIs and those with overweight/obese BMIs-- we will not know until this is examined.

It must also be solidified whether or not creatine can actually be used as a clinical therapeutic method; and whether that usage would be through an increase of dietary creatine

consumption or simply handing a patient creatine monohydrate tablet or powder along with their other disease management prescriptions. Given the prevalence of disease states which have already been investigated regarding creatine supplementation, it might be beneficial to weigh the pros and cons of a dietary shift towards "prescription" within these disease states as well. Whole foods tend to contain more beneficial vitamins and minerals than their pill counterparts which would be beneficial for the management of many disease states, however, Cr is difficult to quantify within individual food items. Supplementation may be the way to go with this compound.

Data on dietary intakes of creatine is also severely lacking. While the vegetarian/vegan vs. non-vegetarian/non-vegan discrepancy is obvious, there were no studies found on varying amounts of creatine between age group, or comparing people living in different parts of the country, much less the world. Regional diets have varying amounts of creatine sources within them, due to cultural, religious, and socioeconomic reasons, so it makes sense that the amount of Cr within endogenous creatine pools-- as well as free creatine-- would vary across the states and nations. Implementing this data collection change would also allow better data on dietary creatine intake to be measured. Perhaps in the future, once clinical relevance of Cr is solidified, creatine will get its chance in the spotlight; a subcategory of the nutrition label, beneath protein.

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