15 Nutraceutical Application of Creatine

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CONTENTS

15.1 Introduction .......................................................................................................................... 267
15.2 Creatine Classification Aspects ............................................................................................ 268
  15.2.1 Nutrient Category ........................................................................................................ 268
  15.2.2 Molecular Characteristics ............................................................................................ 268
  15.2.2.1 Forms of Creatine .................................................................................................... 268
  15.2.2.2 Solubility and Stability ............................................................................................ 269
15.3 Sources of Creatine ............................................................................................................ 270
  15.3.1 Food and Fortification .................................................................................................... 270
  15.3.2 Supplemental Sources ............................................................................................... 271
15.4 Biological Aspects of Creatine .......................................................................................... 272
  15.4.1 Digestion and Absorption ............................................................................................ 272
  15.4.2 Metabolism and Cellular Aspects ............................................................................... 272
  15.4.3 Toxicity and Safety ...................................................................................................... 272
15.5 Nutraceutical/Functional Applications of Creatine ............................................................ 274
  15.5.1 Health Promotion ........................................................................................................ 274
  15.5.2 Disease Prevention and Application ........................................................................... 275
  15.5.2.1 Creatine Synthesis Deficiencies ............................................................................ 275
  15.5.2.2 Neurodegenerative Diseases ................................................................................ 276
  15.5.2.3 Ischemic Heart Disease ......................................................................................... 276
  15.5.2.4 Pregnancy ............................................................................................................... 276
  15.5.3 Physical Performance Aspects .................................................................................... 276
  15.5.3.1 Ergogenic Effects .................................................................................................... 276
  15.5.3.2 Enhanced Recovery ............................................................................................... 277
  15.5.3.3 Injury Prevention .................................................................................................... 279
  15.5.3.4 Enhanced Tolerance to Exercise in the Heat ............................................................ 279
  15.5.3.5 Enhanced Rehabilitation from Injury .................................................................... 280
  15.5.3.6 Brain and Spinal Cord Neuroprotection ................................................................. 280
  15.5.3.7 International Society of Sports Nutrition Position Stand ...................................... 281
15.6 Frontiers in Applications and Research ............................................................................. 282
References ...................................................................................................................................... 282

15.1 INTRODUCTION

Creatine is a member of the guanidine phosphagen family\(^1,2\) and is a naturally occurring nitrogen-containing compound found primarily in red meat and fish\(^3-6\). It is also processed and manufactured into a dietary supplement and used by a variety of exercising and athletic populations (i.e., athletes, aging adults)\(^2,7\). Creatine is one of the most popular dietary supplement ingredients in the sports...
nutrition segment of the over $40-billion global sports nutrition market. Creatine is considered a non-essential nutrient since it can be produced within the human body, and through endogenous production and supplementation, muscle creatine supports high-intensity muscle actions during exercise and athletic performance. Beyond muscle performance, creatine has been shown to have some additional nutraceutical applications, while at the same time there are often questions related to safety. In this chapter, we will review the production of creatine in the body, availability in foods and supplements, and therapeutic applications.

15.2 CREATINE CLASSIFICATION ASPECTS

15.2.1 NUTRIENT CATEGORY

Creatine (N-aminoiminomethyl-N-methyl glycine) is a member of the guanidine phosphagen family. It is a naturally occurring nitrogen containing compound found primarily in red meat and fish. It is also processed and manufactured into a dietary supplement and used by a variety of exercising and athletic populations (i.e., athletes, aging adults). Creatine is one of the most popular dietary supplement ingredients in the sports nutrition segment of the over $40-billion global sports nutrition market.

15.2.2 MOLECULAR CHARACTERISTICS

The chemical structure of creatine and phosphocreatine are presented in Figures 15.1 and 15.2, while Figure 15.3 shows the reversible conversion of creatine to creatinine. Most creatine is stored in the skeletal muscle (~95%) with small amounts also found in the brain and testes (~5%). About two-thirds of intramuscular creatine is phosphocreatine (PCr), with the remaining being free creatine. The total intramuscular creatine pool (PCr + Cr) averages about 120 mmol/kg of dry muscle mass for a 70-kg individual. However, the upper limit of creatine storage appears to be about 160 mmol/kg of dry muscle mass in most individuals. About 1%–2% of intramuscular creatine is degraded into creatinine (metabolic by-product) and excreted in the urine. Therefore, the body needs to replenish about 1–3 grams of creatine per day to maintain normal creatine stores depending on muscle mass.

15.2.2.1 Forms of Creatine

The most common form of creatine found in dietary supplements is monohydrate (CM). As described in detail by Jäger and colleagues, creatine monohydrate is crystallized from water as monoclinic prisms holding one molecule of water of crystallization per molecule of creatine (i.e., creatine

![FIGURE 15.1 Chemical structure of creatine. From Wiki Commons: https://commons.wikimedia.org/wiki/File:Creatine_neutral.png.](https://commons.wikimedia.org/wiki/File:Creatine_neutral.png)

monohydrate). Continued drying of CM results in a loss of the water of crystallization at around 100°C, yielding creatine anhydrous. Creatine is a weak base with a \( pK_B \) value of 11.02 at 25°C. As a result, creatine can only form salts with strong acids, those having a \( pK_A \) value of less than 3.98.\(^1\) Creatine forms salts by the protonation of its guanidine moiety (see Figure 15.3). Creatine salts such as citrate, maleate, fumarate, tartrat,\(^{15}\) pyruvate,\(^{16}\) ascorbate,\(^{17}\) and orotate\(^{18}\) were first introduced to the marketplace as early as the late 1990s. Derivatives of creatine such as creatine ester or even creatine alcohols have also been marketed as dietary supplements. The amount of creatine in different forms of creatine varies. The creatine content of CM is 87.9% of creatine, whereas other forms of creatine have less creatine per volume (see Table 15.1). Commercial creatine salts are formed in solution or by mechanical processes such as milling or grinding under the presence of residual water. Complexes are formed by the subsequent replacement of the solvating molecules by the new ligands.

### 15.2.2.2 Solubility and Stability

Because creatine is an ampholytic amino acid, it is not very soluble in water. The solubility of creatine in water increases with temperature, where 1 liter of water dissolves 6 g of creatine at 4°C.

#### TABLE 15.1

<table>
<thead>
<tr>
<th>Form of Creatine</th>
<th>Creatine Content</th>
<th>Difference to Creatine Monohydrate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatine Anhydrous</td>
<td>100%</td>
<td>14%</td>
</tr>
<tr>
<td>Creatine Monohydrate</td>
<td>88%</td>
<td>0%</td>
</tr>
<tr>
<td>Creatine Ethyl Ester</td>
<td>82%</td>
<td>−6%</td>
</tr>
<tr>
<td>Creatine Maleate (3:1)</td>
<td>75%</td>
<td>−15%</td>
</tr>
<tr>
<td>Creatine Methyl Ester HCl</td>
<td>72%</td>
<td>−18%</td>
</tr>
<tr>
<td>Creatine Citrate (3:1)</td>
<td>66%</td>
<td>−25%</td>
</tr>
<tr>
<td>Creatine Malate (2:1)</td>
<td>66%</td>
<td>−25%</td>
</tr>
<tr>
<td>Creatine Pyruvate</td>
<td>60%</td>
<td>−32%</td>
</tr>
<tr>
<td>Creatine a-Amino Butyrate</td>
<td>56%</td>
<td>−36%</td>
</tr>
<tr>
<td>Creatine a-Ketoglutarate</td>
<td>54%</td>
<td>−39%</td>
</tr>
<tr>
<td>Sodium Creatine Phosphate</td>
<td>51%</td>
<td>−42%</td>
</tr>
<tr>
<td>Creatine Taurinate</td>
<td>51%</td>
<td>−42%</td>
</tr>
<tr>
<td>Creatine Pyroglutamate</td>
<td>51%</td>
<td>−42%</td>
</tr>
<tr>
<td>Creatine Ketoisocaproate</td>
<td>50%</td>
<td>−43%</td>
</tr>
<tr>
<td>Creatine Orotate (3:1)</td>
<td>46%</td>
<td>−48%</td>
</tr>
<tr>
<td>Carnitine Creatinate</td>
<td>45%</td>
<td>−49%</td>
</tr>
<tr>
<td>Creatine Decanoate</td>
<td>43%</td>
<td>−51%</td>
</tr>
<tr>
<td>Creatine Gluconate</td>
<td>40%</td>
<td>−54%</td>
</tr>
</tbody>
</table>

The solubility of creatine also increases with lowering of pH. In this regard, CM dissolves 14 g/L at 20°C, resulting in a neutral pH of 7. Comparatively, tricreatine citrate in water has a pH of 3.2, and creatine pyruvate has a pH of 2.6. As a result, creatine citrate dissolves 29 g/L at 20°C, while creatine pyruvate dissolves 54 g/L at 20°C. When normalized by the relative amount of creatine per molecule, creatine citrate (19.14 g/L) and creatine pyruvate (32.4 g/L) show a 1.55- and 2.63-fold better solubility, respectively, when compared to CM (12.3 g/L). On the other hand, creatinol-O-phosphate (5 g/L at 20°C) has inferior solubility, while dicreatinol sulfate (1,370 g/L at 20°C) shows superior solubility when compared to CM, creatine salts, or creatine esters.

In terms of stability, CM powder is very stable, showing no signs of degradation over years, even at elevated temperatures. However, creatine is not stable in aqueous solution due to an intramolecular cyclization. The lower the pH and higher the temperature, the faster creatine is degraded to creatinine. The degradation of creatine can be reduced or even halted by either lowering the pH under 2.5 or increasing the pH. In this regard, a very high pH results in the deprotonation of the acid group, thereby slowing down the degradation process by making intramolecular cyclization more difficult. A very low pH results in the protonation of the amide function of the creatine molecule, thereby preventing intra-molecular cyclization (see Figure 15.4). This effect also occurs under the acidic conditions in the stomach, hence preventing the breakdown of creatine. Because of this, the conversion of creatine to creatinine in the gastrointestinal tract is minimal regardless of transit time.

### 15.3 SOURCES OF CREATINE

#### 15.3.1 Food and Fortification

The body turns over about 1%-2% of its creatine pool per day (i.e., 1-2 g/d) depending on the level of physical activity. About half of the daily need for creatine is obtained from the diet. As shown in Table 15.2, most dietary creatine is obtained from red meat and fish. For example, one pound (16 ounces, approximately 0.5 kg) of uncooked beef and salmon provides about 1 to 2 grams of creatine. The remaining amount of creatine is synthesized primarily in the liver and kidneys from arginine and glycine by the enzyme arginine glycine amidinotransferase (AGAT) to guanidinoacetate (GAA), which is then methylated by guanidinoacetate N-methyltransferase.
Nutraceutical Application of Creatine

271

TABLE 15.2
Creatine Content of Foods

<table>
<thead>
<tr>
<th>Food</th>
<th>g/lb</th>
<th>g/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shrimp</td>
<td>Trace</td>
<td>Trace</td>
</tr>
<tr>
<td>Cod</td>
<td>1.4</td>
<td>3</td>
</tr>
<tr>
<td>Tuna</td>
<td>1.8</td>
<td>4</td>
</tr>
<tr>
<td>Salmon</td>
<td>2</td>
<td>4.5</td>
</tr>
<tr>
<td>Herring</td>
<td>3–4.5</td>
<td>6.5–10</td>
</tr>
<tr>
<td>Beef</td>
<td>2</td>
<td>4.5</td>
</tr>
<tr>
<td>Pork</td>
<td>2.3</td>
<td>5</td>
</tr>
<tr>
<td>Cranberries</td>
<td>0.01</td>
<td>0.02</td>
</tr>
<tr>
<td>Milk</td>
<td>0.05</td>
<td>0.1</td>
</tr>
</tbody>
</table>


(GAMT) using S-adenosyl methionine to form creatine (see Figure 15.4). Some individuals have been found to have creatine synthesis deficiencies due to inborn errors in AGAT, GMAT, and/or creatine transporter (CRTR) deficiencies and therefore must depend on dietary creatine intake to maintain normal muscle and brain concentrations of PCr and Cr. Vegetarians have been reported to have lower intramuscular creatine stores (90–110 mmol/kg of dry muscle) and therefore may observe greater gains in muscle creatine content from creatine supplementation. Conversely, larger athletes engaged in intense training may need to consume 5–10 g/day of creatine to maintain optimal whole-body creatine stores, and clinical populations may need to consume 10–30 g/day throughout their lifespan to offset creatine synthesis deficiencies and/or provide therapeutic benefit in various disease states.

15.3.2 SUPPLEMENTAL SOURCES

In a typical omnivore diet that contains 1–2 g/day of creatine, muscle creatine stores achieve approximately 60%–80% saturation. Therefore, dietary supplementation of creatine serves to increase muscle creatine and PCr by 20%–40% (see Figure 15.5). The most effective way to increase muscle creatine stores is to ingest 5 grams of creatine monohydrate (or approximately 0.3 g/kg body weight) four times daily for 5–7 days. However, higher levels of creatine supplementation for longer periods of time may be needed to increase brain concentrations of creatine, offset creatine synthesis deficiencies, or influence disease states. Once muscle creatine stores are fully saturated, creatine stores can generally be maintained by ingesting 3–5 g/day, although some studies indicate that larger athletes may need to ingest as much as 5–10 g/day in order to maintain creatine stores. An alternative supplementation protocol is to ingest 3 g/day of creatine monohydrate for 28 days. However, this method would only result in a gradual increase in muscle creatine content compared to the more rapid loading method and may therefore have less effect on

FIGURE 15.5 Cycling of creatine to creatinine. From Wiki Commons: https://upload.wikimedia.org/wikipedia/commons/b/bd/Cyclization_of_Creatine.svg
exercise performance and/or training adaptations until creatine stores are fully saturated. Research has shown that once creatine stores in the muscle are elevated, it generally takes 4 to 6 weeks for creatine stores to return to baseline. Additionally, it has been recommended that due to the health benefits of creatine, individuals should consume about 3 g/day of creatine in their diet, particularly as one ages. No evidence has suggested that muscle creatine levels fall below baseline after cessation of creatine supplementation; therefore, the potential for long-term suppression of endogenous creatine synthesis does not appear to occur.

15.4 BIOLOGICAL ASPECTS OF CREATINE

15.4.1 DIGESTION AND ABSORPTION

Because creatine is not degraded at low pH levels, less than 1% of creatine monohydrate is degraded to creatinine as it passes through the gastrointestinal tract. Creatine transport into cells occurs through a CRTR that is both sodium and insulin dependent. Ingesting creatine with carbohydrate or a combination of carbohydrate and protein has been reported to more consistently promote greater creatine retention.

15.4.2 METABOLISM AND CELLULAR ASPECTS

Phosphagens are prevalent in all species and play an important role in maintaining energy availability. The primary metabolic role of creatine is to combine with a phosphoryl group (Pi) to form PCr through the enzymatic reaction of creatine kinase (CK). Wallimann and colleagues suggested that the pleiotropic effects of Cr are mostly related to the functions of CK and PCr (i.e., CK/PCr system). As adenosine triphosphate (ATP) is degraded into adenosine diphosphate (ADP) and Pi to provide free energy for metabolic activity; additionally, the free energy released from the hydrolysis of PCr into Cr + Pi can be used as a buffer to resynthesize ATP. This helps maintain ATP availability, particularly during maximal effort anaerobic sprint-type exercise. The CK/PCr energy shuttle connects sites of ATP production (glycolysis and mitochondrial oxidative phosphorylation) with subcellular sites of ATP utilization (ATPases). In this regard, creatine enters the cytosol through a CRTR. In the cytosol, creatine and associated cytosolic and glycolytic CK isoforms help maintain glycolytic ATP levels, the cytosolic ATP/ADP ratio, and cytosolic ATP-consumption. Additionally, creatine diffuses into the mitochondria and couples with ATP produced from oxidative phosphorylation and the adenine nucleotide translocator (ANT) via mitochondrial CK (see Figure 15.6). ATP and PCr can then diffuse back into the cytosol and help buffer energy needs. This coupling also reduces the formation of reactive oxygen species and can therefore act as a direct and/or indirect antioxidant.

The CK/PCr energy shuttle thereby connects sites of ATP production (glycolysis and mitochondrial oxidative phosphorylation) with subcellular sites of ATP utilization (ATPases) in order to fuel energy metabolism. In this way, the CK/PCr system thereby serves as an important regulator of metabolism, which may help explain the ergogenic and potential therapeutic health benefits of creatine supplementation.

15.4.3 TOXICITY AND SAFETY

Since creatine monohydrate became a popular dietary supplement in the early 1990s, over 1000 studies have been conducted and billions of servings of creatine have been ingested. The only consistently reported side effect from creatine supplementation that has been described in the literature has been weight gain. Available short- and long-term studies in healthy and diseased populations, from infants to the elderly, at dosages ranging from 0.1 to 0.8 g/kg/day for up
FIGURE 15.6 Proposed creatine kinase/phosphocreatine (CK/PCr) energy shuttle. Abbreviations: CRT = creatine transporter; ANT = adenine nucleotide translocator; ATP = adenine triphosphate; ADP = adenine diphosphate; OP = oxidative phosphorylation; mtCK = mitochondrial creatine kinase; G = glycolysis; CK-g = creatine kinase associated with glycolytic enzymes; CK-c = cytosolic creatine kinase; CK-a = creatine kinase associated with subcellular sites of ATP utilization; 1–4 sites of CK/ATP interaction. (From Kreider RB. J Int Soc Sports Nutr. 2017;14:18; Kreider RB, Jung YP. J Exerc Nutr Biochem. 2011;15:53–69.)

FIGURE 15.7 Role of mitochondrial creatine kinase (mtCK) in high energy metabolite transport and cellular respiration. Abbreviations: VDAC = voltage-dependent anion channel; ROS = reactive oxygen species; RNS = reactive nitrogen species; ANT = adenine nucleotide translocator; ATP = adenine triphosphate; ADP = adenine diphosphate; Cr = creatine; and, PCr = phosphocreatine interaction. (From Kreider RB. J Int Soc Sports Nutr. 2017;14:18; Kreider RB, Jung YP. J Exerc Nutr Biochem. 2011;15:53–69.)
to 5 years have consistently shown that creatine supplementation poses no adverse health risks and may provide a number of health and performance benefits. Additionally, adverse event assessments related to dietary supplementation, including in pediatric populations, have revealed that creatine was rarely mentioned and was not associated with any significant number or any consistent pattern of adverse events.\textsuperscript{74–76} The breadth and repetition of these findings provide compelling evidence that creatine monohydrate is well tolerated and safe to consume in healthy untrained and trained individuals regardless of age. For these reasons, it is no wonder that Wallimann and colleagues\textsuperscript{43} recommended that individuals should consume 3 g/day of creatine throughout the lifespan to promote general health.

15.5 NUTRACEUTICAL/FUNCTIONAL APPLICATIONS OF CREATINE

15.5.1 HEALTH PROMOTION

Although creatine supplementation has been primarily been viewed as an ergogenic aid for athletes, a number of health benefits have also been identified with creatine use. For example, there is growing evidence that creatine supplementation may improve health status as individuals age.\textsuperscript{65,67–69,77} In this regard, creatine supplementation has been reported to help lower cholesterol and triglyceride levels,\textsuperscript{78,79} reduce fat accumulation in the liver,\textsuperscript{80} reduce homocysteine levels,\textsuperscript{81} serve as an antioxidant,\textsuperscript{82–85} enhance glycemic control,\textsuperscript{86–89} slow tumor growth in some types of cancers,\textsuperscript{47,56,81,90} increase strength and/or muscle mass,\textsuperscript{61,65,68,69,91–96} minimize bone loss,\textsuperscript{95,96} improve functional capacity in patients with knee osteoarthritis\textsuperscript{97} and fibromyalgia,\textsuperscript{98} positively influence cognitive function,\textsuperscript{67,77,99} and in some instances serve as an antidepressant.\textsuperscript{100–102}

For example, Gualano and associates\textsuperscript{103} supplemented patients with type II diabetes with a placebo or creatine (5 g/day) for 12 weeks during training. Creatine supplementation significantly decreased HbA1c and glycemic response to a standardized meal as well as increased GLUT-4 translocation. These findings suggest that creatine supplementation combined with an exercise program improves glycemic control and glucose disposal in type 2 diabetic patients.

The European Working Group on Sarcopenia in Older People (EWGSOP2) has recently defined sarcopenia as a muscle disease (ICD-10-MC Diagnosis Code) characterized by low muscle strength, muscle mass, and functionality (Cruz-Jentoft et al.).\textsuperscript{104} Typically, adults lose between 1%–2% of their total muscle mass per year after the age of 50, which corresponds to a 1.5% decrease in maximal strength.\textsuperscript{105} Three meta-analyses indicate that creatine supplementation during resistance training increases muscle accretion by 1.2 kg more than placebo during training.\textsuperscript{94,106,107} Furthermore, creatine supplementation during resistance training leads to greater gains in muscle strength,\textsuperscript{94,106,107} has the potential to improve indices of functionality\textsuperscript{245} and decreases body fat in aging adults compared to placebo during resistance training.\textsuperscript{110}

Regarding bone biology, Chilibeck et al.\textsuperscript{96} showed that postmenopausal women (>50 years of age) who supplemented with creatine (0.1 g/kg/day) during 52 weeks of whole-body resistance training experienced an attenuated rate of bone mineral density loss in the femoral neck and an increase in femoral shaft width compared to placebo. Previous work from the same laboratory showed that 12 weeks of creatine supplementation (0.3 g/kg for 5 days, 0.07 g/kg thereafter) during whole-body resistance training in aging males (>50 years of age) increased upper-limb bone mineral content by 3.2% compared to a non-significant decrease for the placebo group (Chilibeck et al.).\textsuperscript{108} While the mechanistic actions explaining the positive effect from creatine on bone remain to be elucidated, creatine may increase osteoblast cell activity\textsuperscript{109} and reduce urinary excretion of cross-linked n-telopeptides of Type I collagen, an indicator of bone resorption.\textsuperscript{95,111–113} Results across studies suggest creatine has anabolic and anti-catabolic effects on bone.

Finally, a number of studies have shown that creatine supplementation can increase brain creatine content generally by 5%–15%.\textsuperscript{114–116} Moreover, creatine supplementation can reduce mental fatigue\textsuperscript{117} and/or improve cognitive function.\textsuperscript{99,118–121} For example, Watanabe et al.\textsuperscript{117} reported that creatine...
supplementation (8 g/day for 5 days) reduced mental fatigue when subjects repeatedly performed a simple mathematical calculation and increased oxygen utilization in the brain. Rae and colleagues\textsuperscript{118} reported that creatine supplementation (5 g/day for 6 weeks) significantly improved working memory and intelligence tests requiring speed of processing. McMorris and coworkers\textsuperscript{120} found that creatine supplementation (20 g/day for 7 days) after sleep deprivation demonstrated significantly less decrement in performance in random movement generation, choice reaction time, balance, and mood state, suggesting that creatine improves cognitive function in response to sleep deprivation. This research group also examined the effects of creatine supplementation (20 g/day for 7 days) on cognitive function in elderly participants and found that creatine supplementation significantly improved performance on random number generation, forward spatial recall, and long-term memory tasks. Ling and associates\textsuperscript{121} reported that creatine supplementation (5 g/day for 15 days) improved cognition on some tasks. Since creatine uptake by the brain is slow and limited, current research is investigating whether dietary supplementation of creatine precursors like GAA may promote greater increases in brain creatine.\textsuperscript{122,123} One recent study suggested that GAA supplementation (3 g/day) increased brain creatine content to a greater degree than creatine monohydrate.\textsuperscript{123} In summary, multiple studies have provided evidence that creatine supplementation in varying populations can improve cognition, executive function, recall, memory, and brain creatine levels.

15.5.2 Disease Prevention and Application

Given the role of creatine in metabolism, performance, and training adaptations, a number of researchers have been investigating the potential therapeutic benefits of creatine supplementation in various clinical populations. The following highlights some of these applications.

15.5.2.1 Creatine Synthesis Deficiencies

Creatine deficiency syndromes are a group of inborn errors (e.g., AGAT deficiency, GAMT deficiency, and CRTR deficiency) that reduce or eliminate the ability to endogenously synthesize or effect transcellular creatine transport.\textsuperscript{32} Individuals with creatine synthesis deficiencies have low levels of creatine and PCr in the muscle and the brain. As a result, they often have clinical manifestations of muscle myopathies, gyrate atrophy, movement disorders, speech delay, autism, mental retardation, epilepsy, and developmental problems.\textsuperscript{28,32,124} For this reason, a number of studies have investigated the use of relatively high doses of creatine monohydrate supplementation (e.g., 0.3–0.8 g/kg/day, equivalent to 21–56 g/day of creatine for a 70-kg person, or 1–2.7 times greater than the adult loading dose) throughout the lifespan as a means of treating children and adults with creatine synthesis deficiencies.\textsuperscript{28,32,45,124–127} These studies generally show some improvement in clinical outcomes, particularly for AGAT and GAMT, with less consistent effects on CRTR deficiencies.\textsuperscript{124} For example, Battini et al.\textsuperscript{128} reported that a patient diagnosed at birth with AGAT deficiency who was treated with creatine supplementation beginning at 4 months of age experienced normal psychomotor development at 18 months compared to siblings who did not have the deficiency. Stockler-Ipsiroglu and coworkers\textsuperscript{129} evaluated the effects of creatine monohydrate supplementation (0.3–0.8 g/kg/day) in 48 children with GMAT deficiency with clinical manifestations of global developmental delay/intellectual disability (DD/ID) with speech/language delay and behavioral problems (n = 44), epilepsy (n = 35), or movement disorder (n = 13). The median age at treatment was 25.5 months, 39 months, and 11 years in patients with mild, moderate, and severe DD/ID, respectively. The researchers found that creatine supplementation increased brain creatine levels and improved or stabilized clinical symptoms. Moreover, four patients treated younger than 9 months had normal or almost normal developmental outcomes.

Long-term creatine supplementation has also been used to treat patients with creatine deficiency-related gyrate atrophy.\textsuperscript{130–134} These findings and others provide promise that high-dose creatine monohydrate supplementation may be an effective adjunctive therapy for children and adults with creatine synthesis deficiencies.\textsuperscript{33,124,135–137} Additionally, these reports provide strong evidence
regarding the long-term safety and tolerability of high-dose creatine supplementation in pediatric populations with creatine synthesis deficiencies, including infants less than 1 year of age.\textsuperscript{135}

15.5.2.2 Neurodegenerative Diseases

A number of studies have investigated the short- and long-term therapeutic benefit of creatine supplementation in children and adults with various neuromuscular diseases like muscular dystrophies,\textsuperscript{11,12,138–141} Huntington's disease,\textsuperscript{38,142–147} Parkinson's disease,\textsuperscript{38,64,142,148–150} mitochondria-related diseases,\textsuperscript{55,151–153} and amyotrophic lateral sclerosis (a.k.a. Lou Gehrig's Disease).\textsuperscript{52,154–160} An excellent summary study was completed by Bender and colleagues\textsuperscript{38} and reported results of several large clinical trials evaluating the effects of creatine supplementation in patients with Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS). A total of 1687 patients took an average of 9.5 g/day of creatine for a total of 5480 patient years. Results revealed no clinical benefit on patient outcomes in patients with PD or ALS. However, there was some evidence that creatine supplementation slowed down progression of brain atrophy in patients with HD (although clinical markers were unaffected). Whether creatine supplementation may have a role in mediating other clinical markers in these patient populations and/or whether individual patients may respond more positively to creatine supplementation than others, both remain to be determined. Nevertheless, studies have shown that creatine supplementation in children and adults with neurodegenerative conditions is apparently safe and well tolerated when taking up to 30 g/day for 5 years.

15.5.2.3 Ischemic Heart Disease

Creatine and phosphocreatine play an important role in maintaining myocardial bioenergetics during ischemic events.\textsuperscript{57} For this reason, there has been interest in assessing the role of creatine or phosphocreatine in reducing arrhythmias and/or improving heart function during ischemia.\textsuperscript{161–170} In this respect, Balestrino and colleagues\textsuperscript{57} concluded that phosphocreatine administration, primarily as an addition to cardioplegic solutions, has been used to treat myocardial ischemia and prevent ischemia-induced arrhythmia while improving cardiac function, with some success. They suggested that creatine supplementation may protect the heart during an ischemic event. Thus, prophylactic creatine supplementation may be beneficial for patients at risk for myocardial ischemia and/or stroke.

15.5.2.4 Pregnancy

Since creatine supplementation has been shown to improve brain and heart bioenergetics during ischemic conditions and possess neuroprotective properties, there has been recent interest in the use of creatine during pregnancy to promote neural development and reduce complications resulting from birth asphyxia.\textsuperscript{171–180} The rationale for creatine supplementation during pregnancy is that the fetus relies upon placental transfer of maternal creatine until late in pregnancy and significant changes in creatine synthesis and excretion occur as pregnancy progresses.\textsuperscript{173,175} Consequently, there is an increased demand for and utilization of creatine during pregnancy. Maternal creatine supplementation has been reported to improve neonatal survival and organ function following birth asphyxia in animals.\textsuperscript{171,172,174,176–178,180} Human studies show changes in the maternal urine and plasma creatine levels across pregnancy and association with maternal diet.\textsuperscript{173,175} Consequently, it has been postulated that there may be benefit to creatine supplementation during pregnancy on fetal growth, development, and health.\textsuperscript{173,175} This area of research may have broad implications for fetal and child development and health.

15.5.3 Physical Performance Aspects

15.5.3.1 Ergogenic Effects

Table 15.3 presents the reported ergogenic benefits of creatine supplementation. A large body of evidence now indicates that creatine supplementation increases muscle availability of creatine and PCr and can therefore enhance acute exercise capacity and training adaptations in adolescents.\textsuperscript{181–185}
Nutraceutical Application of Creatine

277

TABLE 15.3
Potential Ergogenic Benefits of Creatine Supplementation

- Increased single and repetitive sprint performance
- Increased work performed during sets of maximal effort muscle contractions
- Increased muscle mass and strength adaptations during training
- Enhanced glycogen synthesis
- Increased anaerobic threshold
- Possible enhancement of aerobic capacity via greater shuttling of ATP from mitochondria
- Increased work capacity
- Enhanced recovery
- Greater training tolerance


Younger adults, older individuals These adaptations would allow an athlete to do more work over a series of sets or sprints, leading to greater gains in strength, muscle mass, and/or performance due to an improvement in the quality of training. Table 15.4 presents the types of sport events in which creatine supplementation has been reported to benefit. Creatine supplementation has primarily been recommended as an ergogenic aid for power/strength athletes to help them optimize training adaptations or athletes who need to sprint intermittently and recover during competition (e.g., American football, soccer, basketball, tennis, etc.). After creatine loading, performance of high intensity and/or repetitive exercise is generally increased by 10%–20% depending on the magnitude of increase in muscle PCr. Benefits have been reported in men and women, although the majority of studies have been conducted on men, and some studies suggest that women may not see as much gain in strength and/or muscle mass during training in response to creatine supplementation. However, as will be described below, a number of other applications in sport may benefit athletes involved in high-intensity intermittent activities as well as endurance events. In terms of performance, the International Society of Sports Nutrition (ISSN) has concluded in its position stand on creatine supplementation that creatine monohydrate is the most effective ergogenic nutritional supplement currently available to athletes in terms of increasing high-intensity exercise capacity and lean body mass during training. Recent position stands by the American Dietetic Association, Dietitians of Canada, and the American College of Sports Medicine on nutrition for athletic performance all drew similar conclusions. Thus, a widespread consensus now exists in the scientific community that creatine supplementation can serve as an effective nutritional ergogenic aid that may benefit athletes involved in numerous sports as well as individuals involved in exercise training.

15.5.3.2 Enhanced Recovery
Creatine supplementation can help athletes recover from intense training. For example, Green and coworkers reported that co-ingesting creatine (5 g) with large amounts of glucose (95 g) enhanced creatine and carbohydrate storage in muscle. Additionally, Steenge et al. reported that co-ingesting creatine (5 g) with 47–97 g of carbohydrate and 50 g of protein enhanced creatine retention. Nelson and colleagues reported that creatine loading prior to performing an exhaustive exercise bout and glycogen loading promoted greater glycogen restoration than just carbohydrate loading alone. Since glycogen replenishment is important to promoting recovery and preventing overtraining during intensified training periods, creatine supplementation may help athletes who deplete large amounts of glycogen during training and/or performance to maintain optimal glycogen levels. Evidence also suggests that creatine supplementation may reduce muscle damage and/or enhance recovery from intense exercise. For example, Cooke and associates evaluated the effects of
creatine supplementation on muscle force recovery and muscle damage following intense exercise. They reported that participants supplemented with creatine had significantly greater isokinetic (+10%) and isometric (+21%) knee extension strength during recovery from exercise-induced muscle damage. Additionally, plasma CK levels were significantly lower (−84%) after 2, 3, 4, and 7 days of recovery in the creatine supplemented group compared to controls. The authors concluded that creatine improved the rate of recovery of knee extensor muscle function after injury. Santos and coworkers\textsuperscript{208} evaluated the effects of creatine loading in experienced marathon runners prior to performing a 30-km race on inflammatory markers and muscle soreness. The researchers reported that creatine loading attenuated the changes in CK (−19%), prostaglandin E2 (−61%), and tumor necrosis factor (TNF) alpha (−34%) and abolished the increase in lactate dehydrogenase (LDH) compared to controls. Similar findings were reported by Demince et al.,\textsuperscript{209} who reported that creatine supplementation inhibited the increase of inflammatory markers (TNF-alpha and C-reactive protein) in response to intermittent anaerobic sprint exercise. Finally, Volek and colleagues\textsuperscript{196} evaluated the effects of creatine supplementation (0.3 g/kg/d) for 4 weeks during an intensified overreaching

<table>
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<th>TABLE 15.4</th>
<th>Examples of Sport Events That May Be Enhanced by Creatine Supplementation</th>
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| Increased PCr | • Track sprints: 60–200 m  
|              | • Swim sprints: 50 m  
|              | • Pursuit cycling |
| Increased PCr Resynthesis | • Basketball 
|                            | • Field hockey 
|                            | • America football 
|                            | • Ice hockey 
|                            | • Lacrosse 
|                            | • Volleyball |
| Reduced Muscle Acidosis | • Downhill skiing 
|                          | • Water sports (e.g., rowing, canoe, kayak, stand-up paddling) 
|                          | • Swim events: 100, 200 m 
|                          | • Track events: 400, 800 m 
|                          | • Combat sports (e.g., MMA, wrestling, boxing, etc.) |
| Oxidative Metabolism | • Basketball 
|                     | • Soccer 
|                     | • Team handball 
|                     | • Tennis 
|                     | • Volleyball 
|                     | • Interval training in endurance athletes |
| Increased Body Mass/Muscle Mass | • American football 
|                              | • Bodybuilding 
|                              | • Combat sports (e.g., MMA, wrestling, boxing, etc.) 
|                              | • Powerlifting 
|                              | • Rugby 
|                              | • Track/field events (shot put; javelin; discus; hammer throw) 
|                              | • Olympic weightlifting |
period followed by a 2-week taper. The researchers found that creatine supplementation was effective in maintaining muscular performance during the initial phase of high-volume resistance training overreaching that otherwise results in small performance decrements. These findings suggest that creatine supplementation can help athletes tolerate heavy increases in training volume. Therefore, there is strong evidence that creatine supplementation can help athletes enhance glycogen loading; experience less inflammation and/or muscle enzyme efflux following intense exercise, and tolerate high volumes of training and/or overreaching to a greater degree, thereby promoting recovery.

15.5.3.3 Injury Prevention
Several studies have reported that creatine supplementation during training and/or competition either has no effect or reduces the incidence of musculoskeletal injury, dehydration, and/or muscle cramping. For example, several initial studies on creatine supplementation provided 15–25 g/day of creatine monohydrate for 4 to 12 weeks in athletes engaged in heavy training with no reported side effects. Kreider and colleagues reported that American collegiate football players ingesting 20 or 25 g/day of creatine monohydrate with a carbohydrate/protein supplement for 12 weeks during off-season conditioning and spring football practice experienced greater gains in strength and muscle mass with no evidence of any adverse side effects. Additionally, in a study specifically designed to assess the safety of creatine supplementation, American collegiate football players ingesting about 16 g/day of creatine for 5 days and 5–10 g/day for 21 months had no clinically significant differences among creatine users and controls in markers of renal function, muscle and liver enzymes, markers of catabolism, electrolytes, blood lipids, red blood cell status, lymphocytes, urine volume, clinical urinalysis, or urine-specific gravity. Meanwhile, creatine users experienced less incidence of cramping, heat illness/dehydration, muscle tightness, muscle strains/pulls, non-contact injuries, total injuries, and missed practices than those not taking creatine.

Similar findings were reported by Greenwood and coworkers, who examined injury rates during a 4-month American collegiate football season among creatine users (0.3 g/kg/day for 5 days, 0.03 g/kg/day for 4 months) and non-users. The researchers reported that creatine users experienced significantly less incidence of muscle cramping, heat illness/dehydration, muscle tightness, muscle strains, and total injuries compared to athletes who did not supplement their diet with creatine. Likewise, Cancela and associates reported that creatine supplementation (15 g/day × 7 d, 3 g/day × 49 d) during soccer training promoted weight gain, but that those taking creating had no negative effects on blood and urinary clinical health markers. Finally, Schroder et al. evaluated the effects of ingesting creatine (5 g/day) for three competitive seasons in professional basketball players. The researchers found that long-term low-dose creatine monohydrate supplementation did not promote clinically significant changes in health markers or side effects. Thus, contrary to unsubstantiated reports, the peer-reviewed literature demonstrates that there is no evidence that: (1) creatine supplementation increases the anecdotally reported incidence of musculoskeletal injuries, dehydration, muscle cramping, gastrointestinal upset, renal dysfunction, and so on, or that (2) long-term creatine supplementation results in any clinically significant side effects among athletes during training or competition for up to 3 years. If anything, evidence reveals that athletes who take creatine during training and competition experience a lower incidence of injuries compared to athletes who do not supplement their diet with creatine.

15.5.3.4 Enhanced Tolerance to Exercise in the Heat
Like carbohydrate, creatine monohydrate has osmotic properties that help retain a small amount of water. For example, initial studies that spanned 5 to 7 days reported that creatine loading promoted fluid retention (e.g., about 0.5–1.0 L) that was generally proportional to the acute weight gain observed. For this reason, there was interest in determining if creatine supplementation may help hyper-hydrate an athlete and/or improve exercise tolerance when exercising in the heat. For example, Volek and colleagues evaluated the effects of creatine supplementation (0.3 g/kg/day for 7 days) on acute cardiovascular, renal, temperature, and fluid-regulatory hormonal responses
to exercise for 35 minutes in the heat. The researchers reported that creatine supplementation augmented repeated sprint cycle performance in the heat without altering thermoregulatory responses. Kilduff and associates\textsuperscript{224} evaluated the effects of creatine supplementation (20 g/day for 7 days) prior to performing exercise to exhaustion at 63% of peak oxygen uptake in the heat (30.3°C). The researchers reported that creatine supplementation increased intracellular water and reduced thermoregulatory and cardiovascular responses to prolonged exercise (e.g., heart rate, rectal temperature, sweat rate), thereby promoting hyper-hydration and a more efficient thermoregulatory response during prolonged exercise in the heat. Watson and colleagues\textsuperscript{218} reported that short-term creatine supplementation (21.6 g/day for 7 days) did not increase the incidence of symptoms or compromise hydration status or thermoregulation in dehydrated (−2%), trained men exercising in the heat. Similar findings were observed by several other groups,\textsuperscript{219,220,228,229} leading researchers to add creatine to glycerol as a highly effective hyper-hydrating strategy to help athletes better tolerate exercise in the heat.\textsuperscript{217,221–223,226,227} These findings provide strong evidence that creatine supplementation (with or without glycerol) may serve as an effective nutritional hyper-hydration strategy for athletes engaged in intense exercise in hot and humid environments, thereby reducing risk to heat related-illness.\textsuperscript{9,230}

15.5.3.5 Enhanced Rehabilitation from Injury

Since creatine supplementation has been reported to promote increases in muscle mass and strength, there has been interest in examining the effects of creatine supplementation on muscle atrophy rates as a result of limb immobilization and/or during rehabilitation.\textsuperscript{231} For example, Hespel and coworkers\textsuperscript{232} examined the effects of creatine supplementation (20 g/day down to 5 g/day) on atrophy rates and rehabilitation outcomes in individuals who had their right leg casted for 2 weeks. During the 10-week rehabilitation phase, participants performed three sessions a week of knee extension rehabilitation. The researchers reported that individuals in the creatine group experienced greater changes in the cross-sectional area of muscle fiber (+10%) and peak strength (+25%) during the rehabilitation period. These changes were associated with greater changes in myogenic regulating factor 4 (MRF4) and myogenic protein expression. In a companion paper to this study, Op’t Eijnde et al.\textsuperscript{86} reported that creatine supplementation offset the decline in muscle GLUT4 protein content that occurs during immobilization and increased GLUT4 protein content during subsequent rehabilitation training in healthy subjects. Collectively, these findings suggest that creatine supplementation lessened the amount of muscle atrophy and mitigated detrimental intracellular changes that impact intracellular signaling and glucose handling in skeletal muscle associated with immobilization while promoting greater gains in strength during rehabilitation. Similarly, Jacobs and associates\textsuperscript{233} examined the effects of creatine supplementation (20 g/d for 7 days) on upper extremity work capacity in individuals with cervical-level spinal cord injury (SCI). Results revealed that peak oxygen uptake and ventilatory anaerobic threshold were increased following creatine supplementation. Conversely, Tyler et al.\textsuperscript{234} reported that creatine supplementation (20 g/day for 7 days, and 5 g/day thereafter) did not significantly affect strength or functional capacity in patients recovering from anterior cruciate ligament (ACL) surgery. Moreover, Perret and colleagues\textsuperscript{235} reported that creatine supplementation (20 g/day for 6 days) did not enhance 800-meter wheelchair performance in trained SCI wheelchair athletes. While not all studies show benefit, there is evidence that creatine supplementation may help lessen muscle atrophy following immobilization and promote recovery during exercise-related rehabilitation in some populations. Thus, creatine supplementation may help athletes and individuals with clinical conditions recover from injuries.

15.5.3.6 Brain and Spinal Cord Neuroprotection

The risk of concussions and/or SCI in athletes involved in contact sports has become an international concern among sporting organizations and the public. It has been known for a long time that creatine supplementation possesses neuroprotective benefits.\textsuperscript{55,62,64,236} For this reason, a number of studies have
Nutraceutical Application of Creatine

examined the effects of creatine supplementation on traumatic brain injury (TBI), cerebral ischemia, and SCI. For example, Sullivan et al.\textsuperscript{237} examined the effects of 5 days of creatine administration prior to a controlled TBI in rats and mice. The researchers found that creatine monohydrate ameliorated the extent of cortical damage by 36\%–50\%. The protection appeared to be related to creatine-induced maintenance of neuronal mitochondrial bioenergetics. Therefore, the researchers concluded that creatine supplementation may be useful as a neuroprotective agent against acute and chronic neurodegenerative processes. In a similar study, Haussmann and associates\textsuperscript{238} investigated the effects of rats fed creatine (5 g/100 g dry food) before and after a moderate SCI. The researchers reported that creatine ingestion improved locomotor function tests and reduced the size of scar tissue after the SCI. The authors suggested that pretreatment of patients with creatine may provide neuroprotection in patients undergoing spinal surgery who are at risk of SCI. Similarly, Prass and colleagues\textsuperscript{239} reported findings that creatine administration reduced brain infarct size following an ischemic event by 40\%.

Adcock et al.\textsuperscript{240} reported that neonatal rats fed 3 g/kg of creatine for 3 days observed a significant increase in the ratio of brain PCR to Pi and a 25\% reduction in the volume of edemic brain tissue following cerebral hypoxic ischemia. The authors concluded that creatine supplementation appears to improve brain bioenergetics, thereby helping minimize the impact of brain ischemia. Similarly, Zhu and colleagues\textsuperscript{241} reported that oral creatine administration resulted in a marked reduction in ischemic brain infarction size and neuronal cell death, and provided neuroprotection after cerebral ischemia in mice. The authors suggested that given the safety record of creatine, creatine might be considered a novel therapeutic agent for inhibition of ischemic brain injury in humans. Allah et al.\textsuperscript{242} reported that creatine monohydrate supplementation for 10 weeks reduced the infarction size and improved learning/memory following neonatal hypoxia ischemia encephalopathy in female mice. The authors concluded that creatine supplementation has the potential to improve the neuro-function following neonatal brain damage. Finally, Rabchevsky and associates\textsuperscript{243} examined the efficacy of creatine-supplemented diets on hind limb functional recovery and tissue sparing in adult rats. Rats were fed a control diet or 2\% creatine-supplemented chow for 4–5 weeks prior to and following SCI. Results revealed that creatine feeding significantly reduced loss of gray matter after SCI. These findings provide strong evidence that creatine supplementation may limit damage from concussions, TBI, and/or SCI.\textsuperscript{57,244}

15.5.3.7 International Society of Sports Nutrition Position Stand

After reviewing the scientific and medical literature in this area, in 2017, the International Society of Sports Nutrition concluded the following in terms of creatine supplementation:\textsuperscript{2}

1. Creatine monohydrate is the most effective ergogenic nutritional supplement currently available to athletes with the intent of increasing high-intensity exercise capacity and lean body mass during training.

2. Creatine monohydrate supplementation is not only safe, but has been reported to have a number of therapeutic benefits in healthy and diseased populations ranging from infants to the elderly. There is no compelling scientific evidence that the short- or long-term use of creatine monohydrate (up to 30 g/day for 5 years) has any detrimental effects on otherwise healthy individuals or among clinical populations who may benefit from creatine supplementation.

3. If proper precautions and supervision are provided, creatine monohydrate supplementation in children and adolescent athletes is acceptable and may provide a nutritional alternative with a favorable safety profile to potentially dangerous anabolic androgenic drugs. However, we recommend that creatine supplementation only be considered for use by younger athletes who: (a) are involved in regular, systematic exercise training that is supervised by trained professionals; (b) are consuming a well-balanced and performance enhancing diet; (c) are knowledgeable about appropriate use of creatine; and (d) do not exceed recommended dosages.
4. Label advisories on creatine products that caution against usage by those under 18 years old, while perhaps intended to insulate their manufacturers from legal liability, are likely unnecessary given the science supporting creatine’s safety, including in children and adolescents.

5. At present, creatine monohydrate is the most extensively studied and clinically effective form of creatine for use in nutritional supplements in terms of muscle uptake and ability to increase high-intensity exercise capacity.

6. The addition of carbohydrate or carbohydrate and protein to a creatine supplement appears to increase skeletal muscle uptake of creatine, although the effect on performance measures may not be greater than using creatine monohydrate alone.

7. The quickest method of increasing muscle creatine stores may be to consume \(\sim 0.3 \text{ g/kg/day}\) of creatine monohydrate for 5–7 days followed by 3–5 g/day thereafter to maintain elevated stores. Initially, ingesting smaller amounts of creatine monohydrate (e.g., 3–5 g/day) will increase muscle creatine stores over a 3–4-week period; however, the initial performance effects of this method of supplementation are less supported.

8. Clinical populations have been supplemented with high levels of creatine monohydrate (0.3–0.8 g/kg/day equivalent to 21–56 g/day for a 70-kg individual) for years with no clinically significant or serious adverse events.

9. Further research is warranted to examine the potential medical benefits of creatine monohydrate and precursors like guanidinoacetic acid on sport, health, and medicine.

15.6 FRONTIERS IN APPLICATIONS AND RESEARCH

Creatine monohydrate remains one of the few nutritional supplements for which research has consistently shown ergogenic benefits. Additionally, a number of potential health benefits have been reported from creatine supplementation. While research will continue to evaluate the ergogenic potential, research over the next decade will continue to focus on the role of creatine on general health, aging, disease management, and reduction of disease risk.

REFERENCES


285


