INFORMATION PAPER ON CREATINE AND TRAUMATIC BRAIN INJURY

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RELEVANCE TO THE DEPARTMENT OF DEFENSE

Research to date provides some evidence for the use of creatine supplements to improve outcomes after mild TBI, though both the dose and duration for optimal results remains unknown. Creatine may be useful in environments where warfighters are exposed to acute stressors, such as intense exercise. Given the insufficient evidence, there are no clinical guidelines for using creatine to manage or prevent TBI. Guidance from a healthcare provider or registered performance dietitian is essential before beginning creatine supplements.

KEY POINTS & IMPACT TO THE WARFIGHTER

- Oral consumption of 0.3 grams of creatine monohydrate per kilogram of body weight per day for seven days results in a measurable increase in muscle creatine levels, though increases in brain creatine levels appear to require a higher dose, longer duration of treatment, or both.[1]
    - Creatine uptake by the brain requires a specific transporter protein that is not required for skeletal muscle, and therefore supplementation with higher doses for weeks rather than days may be necessary to produce any effects.[2,3]
    - Guanidinoacetic acid, a precursor of creatine that does not require a transporter protein, might be preferable to creatine monohydrate supplementation.[4]
    - This supplement protocol appears to be beneficial for both men and women, however further study is needed to determine whether women would benefit from different dosages during the menstrual cycle and other periods of hormonal fluctuations.
- Prolonged post-concussion symptoms may be due to the depletion of brain energy stores, thereby providing a biologic rationale for creatine supplementation;[4] however, there are no guidelines for the use of creatine for TBI management at this time.[5]
    - Several small clinical studies provide compelling evidence that creatine supplementation for a week or more may improve or accelerate outcomes following a mild TBI, but to date, there have been no large prospective placebo-controlled randomized trials to establish the efficacy of this treatment.

- Large multi-site prospective randomized trials are necessary to determine the efficacy of creatine for neuroprotection. Future research should consider utilizing objective measurements of brain creatine levels through magnetic resonance spectroscopy, and trials should be designed to determine the optimal dose and duration of creatine supplementation needed under specific stressors.[6]

- Because creatine is not on the DOD Prohibited Dietary Supplement Ingredients list, service members are permitted to use it.[7] However, they should seek guidance from performance dieticians before beginning.[8]

PURPOSE

The purpose of this information paper is to provide a general overview of the current state of the science for using creatine to treat mild TBI and to optimize brain health and performance.

BACKGROUND

Creatine is a popular nutritional aid used among athletes and service members to increase strength and physical performance.[8,9] Creatine monohydrate is the most widely used form[3] and is considered generally recognized as safe by the FDA as a food ingredient for items such as protein bars and powders, energy drinks, powdered drink mixes, and meat substitutes.[10] It is a naturally occurring nitrogenous organic acid produced by the liver, kidneys, pancreas,[8] and brain[11] and is important for maintaining and managing cellular energy stores in both physiological and pathological states. Creatine is highly concentrated in skeletal muscle and the brain, and during activities of high energy demand, it works to increase mitochondrial efficiency to replenish cellular energy.[3,12] Preclinical studies in cell and animal models suggest creatine also may protect against brain damage caused by lack of oxygen to cells, oxidative stress, excessive stimulation of glutamate neurons, and cell death.[11,13-16] To reach the brain, dietary creatine must cross the blood-brain barrier through the creatine transporter protein *SLC6A8*,[11,17] which is also required for creatine to cross the plasma membrane and enter neurons.[18] Because of its low permeability across the blood-brain barrier, the brain relies mainly on its own synthesis of creatine.[11]

Given creatine's involvement in cellular energy production, several studies have used imaging to measure brain creatine levels after TBI. Overall the results are mixed; studies have found both an increase and decrease in brain creatine levels following TBI.[19-21] Some researchers have found areas of the brain with significantly higher levels of creatine in individuals who had sustained a mild TBI than in controls.[22] Using magnetic resonance spectroscopy, others have observed that metabolite profiles within the dorsolateral prefrontal cortex show a lower creatine/choline ratio in mild TBI patients than in controls.[23] In a study of veterans with mild TBI due to blast exposure and memory impairment, the ratio of hippocampal N-acetyl aspartate to creatine levels were significantly lower in the mild TBI group than in controls, indicating potential neuronal damage.[24] Others found that changes in brain creatine levels were most commonly detected when mild TBI was associated with loss of consciousness,[25] although this association has not been found in all studies.[26]

TREATMENT OF TBI WITH CREATINE

After TBI, patients can experience mitochondrial dysfunction, neuropsychological burden, and deficits in cognitive performance.[4] These common sequalae of TBI may involve changes in brain creatine levels, which can result in reduced brain cellular energy levels, glutamate toxicity, and oxidative stress.[4] Accordingly, preliminary data show that creatine-phosphocreatine levels measured after mild TBI can predict cognitive outcomes and emotional distress.[27] Increasing brain creatine levels may be effective for reducing the severity of postconcussive symptoms after mild TBI or enhancing recovery,[4,9,28,29] leading some researchers to promote creatine supplements as a promising option to treat sport-related concussion.[30]

In several clinical studies, creatine supplementation has shown some promise for reducing symptoms of concussion and depression.[31-33] Promising evidence also suggests that creatine effectively restores brain energy following mental fatigue, sleep deprivation, environmental hypoxia, and advanced age.[34] Others have found that creatine may improve recovery from and adaptation to:[4,35]

- Intense training
- Recovery from periods of injury due to extreme inactivity, such as immobilization
- Cognitive processing
- Severity of postconcussive symptoms or recovery from mild TBI

Because creatine is involved in maintaining energy levels in cells with high or fluctuating energy demand, its therapeutic potential relies on an assumption of residual energy impairment in chronic mild TBI.[23] Increasing the availability of creatine in tissue may enhance cellular metabolism and thereby reduce the severity of injury-related symptoms and disease conditions, particularly when oxygen availability is compromised. However, since no published study has investigated how different doses of creatine affects cognition or other post-concussion symptoms, it is unclear what dose and duration of creatine treatment is beneficial.

Several studies have used imaging to measure creatine levels in the brain after supplementation in healthy individuals or in those with TBI.[36-38] In healthy individuals, oral consumption of 20 grams of creatine per day for 1 week[14] to 4 weeks[39] has been shown to significantly increase average brain creatine levels, though the average increase varies by individual. In one small study (n=6) of healthy individuals, the average increase in creatine ranged from 3.5–13.3%, with the smallest increases seen in males with larger body weights.[39]

Because energy provision processes are impaired by certain neurodegenerative disorders,[14] several preclinical and clinical studies have evaluated using creatine to treat neurodegenerative disorders. Although findings from cell and animal models are highly encouraging,[40] most clinical trials have failed to reproduce these positive results.[15] In some small studies, creatine supplementation has shown promise as a safe, effective, and tolerable adjunct to medication for neurologic disorders associated with dysfunctional energy metabolism, such as Huntington's disease and Parkinson's disease.[41,42] Most large randomized clinical trials of creatine treatment for Parkinson's disease, amyotrophic lateral sclerosis, and Huntington's disease have not found any neuroprotective benefit.[13] However, a pilot clinical trial published in 2025 (n=20 patients) found that 20 grams of creatine daily for 8 weeks led to a significant improvement in total cognition, fluid cognition, list-sorting working memory, and oral reading comprehension in individuals diagnosed with dementia due to probable Alzheimer's disease.[43] While these are promising findings, they are preliminary and additional research is warranted to determine the efficacy of creatine as an additional treatment option secondary to current practices. Prophylactic use of creatine for neuroprotection in at-risk populations may be the most promising future direction.[15]

Guanidinoacetic acid, a direct metabolic precursor of creatine, has recently been suggested as a possible alternative to creatine to increase brain creatine levels because it travels more easily across the blood-brain barrier.[44] In an open-label case series (n=5 healthy men), 8 weeks of supplementation with GAA was found to significantly increase creatine levels in the cerebellum and white and gray matter.[45] In another randomized, double-blinded, crossover trial, 14 healthy young men received a GAA-creatine mixture (1 gram of GAA and 3 grams of creatine) or a proportional amount of creatine (4 grams per day) by oral administration for 4 weeks. Those who received the GAA-creatine mixture had a significantly greater increase in the average creatine levels in skeletal muscle and gray matter than those who received creatine alone.[46]

PERFORMANCE OPTIMIZATION

Creatine supplementation could aid cognition by improving brain energy supply and through neuroprotective effects.[47] A systematic review and meta-analysis of randomized controlled trials was conducted to determine the effects of creatine supplementation on memory performance in healthy individuals.[48] In eight studies, the effect of creatine supplementation was compared to that of placebo treatment to measure creatine's impact on memory in healthy individuals. Memory was assessed using the Stroop test, Trail Making Test, Digit Span, delayed recall, and other standardized tests. Overall, creatine supplementation led to greater improvements in memory than the placebo. Further, there was a significantly greater improvement in memory in older adults (66–76 years) than in those 11–31 years of age. Creatine dose (approximately 2.2–20.0 grams per day), duration of intervention (5 days to 24 weeks), sex, or geographical origin did not influence the findings. A separate systematic review that included 16 studies and 492 healthy and diseased populations also investigated the effects of creatine monohydrate administration on cognitive function. Across these studies, there was a significant improvement in memory function, attention time, and processing speed, but no significant effect on overall cognitive function or executive function tasks.[49] These benefits appeared to be greatest for women, those ages 18–60 years, and those with a diagnosed disease (such as fibromyalgia, mild cognitive impairment associated with Parkinson's disease, and chronic schizophrenia). Notably, the duration of supplementation, whether greater than or less than 4 weeks did not significantly impact the results. The variability in these findings may be explained by the difficulty of the cognitive tasks performed; more complex cognitive tasks may be required to observe a positive effect on cognitive performance.[50] Some studies have also suggested that brain creatine levels naturally increase with age, which may contribute to the discrepant findings among TBI studies.[51] Other studies have found improvements in short-term memory and intelligence and reasoning.[52] However, findings related to long-term memory, spatial memory, memory scanning, attention, executive function, response inhibition, word fluency, reaction time, and mental fatigue were inconsistent.[52]

Most protocols involve a loading phase characterized by 20 grams of creatine daily for 1 week followed by a maintenance phase of 3–5 grams per day for a month or longer.[53,54] The optimal dose and duration of creatine supplementation to achieve a cognitive benefit has not been determined, and studies objectively assessing both brain creatine levels and cognitive function are needed.[29] In a case-control study of 20 healthy service members, a loading phase of 0.3 grams of creatine per kilogram of body weight per day for 7 days following 4 weeks of beta-alanine supplementation resulted in greater improvements on physical performance and cognitive processing speed than beta-alanine supplementation alone.[55] Further investigation into the efficacy of both the loading and maintenance phases for cognitive performance and TBI treatment are necessary.

Response to creatine supplementation may depend on age, diet, and the tissue being analyzed. In a study of children, adults, and elderly adults (ages 10–84 years), participants took a placebo followed by creatine (0.3 grams per kilogram of body weight per day) for 7 days.[1] Magnetic resonance spectroscopy showed there was no change in brain creatine levels despite a measurable increase in muscle creatine levels.[1] It appears that higher or more prolonged dosing strategies than those typically used to increase muscle creatine levels may be required to increase brain creatine levels. The optimal dosing strategy to induce this response is currently unknown.[28]

The potential for creatine supplementation to improve cognitive processing may be greatest in conditions of brain creatine deficits, which could be brough on by acute stressors such as: [28,56]

- Exercise
- Sleep deprivation
- Hypoxia, or low oxygen availability to tissue
- During complex and cognitively demanding tasks

In healthy adults, oral administration of a high dose of creatine (20 grams per day for 7 days) has been shown to increase brain creatine levels by an average of 8.0–9.2%, and this increase was capable of improving neuropsychological performance hampered by hypoxia.[14,16] During periods of prolonged exercise in the heat, creatine monohydrate has been shown to promote more efficient regulation of body temperature,[3,40,57] which may improve hydration and mitigate central fatigue, ultimately leading to a lower perception of effort.[57] Some studies have demonstrated that cognitive processing, whether impaired experimentally (such as through sleep deprivation) or naturally (such as due to aging) can be improved with creatine supplementation.[58]

While some studies found no difference between men and women in the therapeutic potential of creatine,[48] sex differences are important to consider because women store 70–80% less creatine than men due to hormone-related changes in creatine kinetics and phosphocreatine resynthesis.[59] Female sex hormones are known to affect key enzymes involved in the endogenous synthesis of creatine, such as creatine kinase.[59] During the follicular phase of the menstrual cycle when estrogen levels are low, creatine kinase activity is also at its lowest. While implications of this require further study, creatine supplementation during the follicular phase may help reduce common menstrual symptoms such as sleep deprivation and lower cognition.[59] Creatine may also help prevent a decrease in physical performance during the menstrual cycle.[60]

ADVERSE EFFECTS

While there have been some reports of weight gain from increased water retention and muscle cramping with creatine supplementation,[61] there are no reports of significant adverse health effects with creatine use in individuals with TBI. Creatinine, a byproduct of creatine metabolism that is filtered by the kidneys and excreted through urine, is an indicator of renal damage when serum levels are elevated.[62] The kidneys also filter urea, another byproduct of protein metabolism that is synthesized in the liver.[62] While urea is not a direct byproduct of creatine metabolism, renal dysfunction as a result of elevated creatinine can secondarily impact blood urea levels. Given this, there are some concerns with liver and kidney damage with high doses of creatine, but recent studies do not show an effect on these organs in healthy individuals.[3,8,40,62] This concern is greater for those with pre-existing kidney or liver disease.[63]

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