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CREATINE IN HUMAN HEALTH: EXERCISE PERFORMANCE AND SELECTED CLINICAL APPLICATIONS

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ABSTRACT

Creatine is a naturally occurring compound synthesized from arginine, glycine, and methionine through a two-step pathway involving arginine:glycine amidinotransferase (AGAT) and guanidinoacetate N-methyltransferase (GAMT). It is transported into cells primarily by the sodium- and chloride-dependent creatine transporter (SLC6A8) and participates in cellular energy buffering through the creatine-phosphocreatine system. Creatine is degraded spontaneously to creatinine, which is eliminated primarily by the kidneys. Creatine monohydrate is well established as an aid to high-intensity exercise and resistance-training adaptations. Research is also examining potential applications in aging and disease, but the strength of evidence varies. A small, single-arm pilot study in people with Alzheimer's disease reported increased brain total creatine and improvement on some cognitive measures; without a control group, it cannot establish that creatine caused those changes. A large clinical trial did not find that creatine slowed clinical progression in Parkinson's disease. Evidence for cognitive, cardiac, and metabolic benefits remains preliminary or mixed. Creatine has not been shown to prevent cancer or age-related chronic diseases in humans. This review summarizes creatine metabolism and transport, evidence related to exercise and selected clinical conditions, and possible interactions with carbohydrate, fenugreek, ashwagandha, and antioxidants. These combinations should not be described as established ways to increase creatine's effectiveness.

KEYWORDS: Creatine; adenosine triphosphate (ATP); creatine transporter; bioenergetics; exercise performance; aging.

INTRODUCTION

Creatine is a naturally occurring compound synthesized from the three amino acids arginine, glycine, and methionine. It is popular among athletes and bodybuilders, and interest in its possible health applications has expanded to the general population. Its best-established uses relate to high-intensity exercise and resistance training. Some people also take creatine in the hope of supporting health during aging, although evidence for disease prevention and other health outcomes is less established. Despite some limitations of creatine use for health benefits, consumers spent more than half billion dollars while globally it was 1.4 billion dollars. A brief history of creatine research helps place current claims in context.[1,2]

History of Discovery of Creatine

In 1832, French chemist Michel Eugène Chevreul isolated a substance from meat and named it creatine, derived from the Greek word kreas, meaning meat. In 1847, Justus von Liebig confirmed that creatine was present in animal muscle; creatinine, a breakdown product of creatine, was also identified in urine during this period. Later studies demonstrated that creatine intake can increase muscle creatine stores. Work in the early twentieth century examined creatine synthesis and supplementation, and by the mid-twentieth century creatine could be synthesized in the laboratory. Subsequent studies found that supplementation, particularly when combined with resistance training, can increase muscle creatine and support training adaptations. Its use in sport became increasingly widespread during the late twentieth century.[3]

Synthesis, Degradation, and Transport of Creatine

Creatine is synthesized endogenously through a two-step

pathway and is converted spontaneously to creatinine, which is eliminated primarily by the kidneys.[4] The first step uses arginine and glycine. In tissues including the kidneys, pancreas, and other organs, AGAT transfers an amidino group from arginine to glycine, producing guanidinoacetate (GAA) and ornithine. GAA then travels through the blood to tissues including the liver, where GAMT methylates it using S-adenosylmethionine (SAM), a compound derived from methionine, as the methyl donor to form creatine.[5,6]

Role of the Creatine Transporter 1 Protein

The creatine transporter, encoded by SLC6A8 and often called CRT-1, facilitates creatine uptake into many cells. It is a sodium- and chloride-dependent transporter. Pathogenic variants in SLC6A8 can cause cerebral creatine deficiency syndrome, which may include intellectual disability, speech and language delays, and seizures.[7-10] Because the transporter is important for cellular uptake, defects can limit creatine entry into affected tissues, including the brain. The extent to which oral creatine can overcome transporter deficiency depends on the underlying defect and should not be assumed.

Can Creatine Prevent Age-Related Decline or Chronic Disease?

We have previously proposed that oxidative stress, chronic inflammation, intestinal dysbiosis, collagen loss, and altered omega-3 fatty-acid status may contribute to declining health during aging and to the development or progression of some chronic diseases, including Alzheimer's disease.[11] This is a proposed framework, not a settled explanation of aging or disease.

Creatine is involved in cellular energy metabolism, but current evidence does not establish that creatine supplementation prevents age-related decline or reduces the risk of chronic diseases. This conclusion should not be interpreted as proof that creatine has no biological effects beyond exercise; rather, any such effects require appropriately designed human studies.

Evidence for Creatine in Selected Conditions

Alzheimer's disease (AD)

A 2025 single-arm pilot study evaluated 20 g/day of creatine monohydrate for eight weeks in 20 people with AD. Brain total creatine increased, and several cognitive test scores improved from baseline. Because the study had no control group, these findings are preliminary and do not establish efficacy. Larger controlled studies are needed.[12] A related single-arm pilot reported increases in some measures of muscle strength and size after the same intervention; these results also require confirmation in controlled trials.[13] It is biologically plausible that altered brain energy metabolism could be relevant to cognition, but the clinical benefit of creatine for AD has not been established.

Parkinson's disease (PD)

A large randomized clinical trial found that creatine monohydrate, taken for at least five years by people with early, treated PD, did not improve clinical outcomes compared with placebo. These findings do not support creatine as a treatment to slow PD progression.[14]

Sarcopenia

Sarcopenia is an age-related condition characterized by loss of muscle strength and muscle quantity, with reduced physical performance in some people. It is multifactorial and may be associated with changes in muscle protein turnover, neuromuscular function, inflammation, physical activity, and nutrition.[15,16] Aging is also associated, on average, with losses in muscle and bone mass and changes in balance and body composition, although the degree and timing vary among individuals.[17-19]

Evidence suggests that creatine supplementation can augment some gains in muscle mass and strength when combined with resistance training, including in older adults. The size of the benefit varies across studies and outcomes. Creatine should not be presented as a stand-alone treatment for sarcopenia, and supplementation does not replace exercise or adequate nutrition.[15,16,19]

Cognitive Function

Creatine and phosphocreatine participate in cellular energy buffering, including in the brain. Some studies have reported increases in brain creatine after supplementation, but the magnitude varies with study design, dose, duration, and participant characteristics.[20-23] Human trials of cognitive outcomes have produced mixed results. Some small studies have reported benefits in selected tasks or under conditions such as sleep deprivation or mental fatigue; these findings do not establish a general cognitive benefit for all adults.[24-28]

For example, a small crossover trial reported improvement on selected memory and reasoning measures after creatine supplementation, while other studies have found limited or inconsistent effects. A study involving sleep deprivation and exercise reported selective effects on some cognitive measures, and research on mental fatigue and sport-specific skills found mixed results across outcomes.[25-28] Further controlled research is needed, particularly in older adults and people with cognitive impairment.

Heart Disease

The heart contains creatine and phosphocreatine, which contribute to cellular energy buffering. This provides a biological rationale for studying creatine in heart disease, but it does not establish that oral creatine treats heart failure or prevents cardiovascular events. In a small trial involving people with chronic heart failure, creatine supplementation did not increase ejection fraction, although skeletal-muscle phosphocreatine and some measures of muscle performance increased.[29] Other

clinical studies have examined creatine with exercise or changes in biomarkers, but the evidence does not establish improvement in major cardiac outcomes.[30]

Accordingly, claims that creatine prevents heart attacks or strokes, improves ejection fraction, or protects the heart from chemotherapy-related injury should not be made based on the the evidence cited here. Creatine is not a substitute for standard cardiovascular care.

Diabetes

A small randomized, double-blind, placebo-controlled trial in people with type 2 diabetes studied creatine in combination with an exercise program. The study reported improvements in glycemic control, including HbA1c, compared with placebo in the exercise context.[31,37] Creatine may influence exercise-related glucose uptake, including through pathways involving GLUT4, but this proposed mechanism does not establish a direct glucose-lowering effect of creatine alone. The evidence remains limited, and creatine should not be considered a diabetes treatment or a replacement for prescribed care.[31,32,37]

Cancer and Antitumor Immunity

Preclinical studies have investigated creatine's role in immune-cell energy metabolism. In mouse models, creatine uptake by CD8+ T cells supported antitumor activity, and creatine supplementation enhanced tumor control in some experimental settings.[33] These findings are not clinical evidence that creatine supplements prevent or treat cancer in humans. An observational analysis of dietary creatine intake and cancer prevalence also cannot establish causation or show that supplementation reduces cancer risk.[34] The role of creatine in cancer biology is complex and may differ by tumor type and context; claims of cancer prevention or treatment are not justified by the current human evidence.

Relationship Between Antioxidants and Creatine

Increased oxidative occurs during exercise, the level of which depends upon the level of exercise. Increased oxidative stress is also associated with age-related chronic diseases. One of the major functions of creatine transporter protein is to take creatine from the blood to the cells. Increased oxidative stress can damage creatine transporter protein which then cannot take creatine to the cells that can lead to depletion of creatine causing reduced energy production. Antioxidants are known to protect against oxidative stress. Therefore, they can protect creatine transporter protein from oxidative stress allowing creatine to enter the cells for energy production.[36] Therefore, I suggest that supplementation of creatine together with antioxidants is essential for producing normal amounts of energy during exercise and older individuals who have elevated oxidative stress.

Factors Proposed to Influence the Effects of Creatine Carbohydrate

Co-ingestion of large amounts of carbohydrate can increase muscle creatine retention under some loading protocols, likely through insulin-mediated effects. This strategy is not necessary for most users taking a regular creatine dose, and it may add substantial calories.[1,2]

Fenugreek (Trigonella foenum-graecum)

One resistance-training study compared creatine plus fenugreek extract with creatine plus a high dose of carbohydrate and reported similar training adaptations over eight weeks.[35] This is a limited evidence base; it does not prove that fenugreek improves creatine absorption or that the combinations are equivalent in all settings.

Ashwagandha (Withania somnifera)

Ashwagandha has been studied separately in relation to stress and exercise outcomes. Evidence that it works synergistically with creatine or increases creatine's effectiveness is not established. Any proposed combination should be presented as a hypothesis rather than a demonstrated effect.

CONCLUSIONS

Creatine monohydrate is widely used by athletes, bodybuilders, and other adults, and its best-established benefits relate to high-intensity exercise and resistance-training adaptations. Creatine synthesis uses arginine, glycine, and methionine and involves AGAT and GAMT. Creatine is converted spontaneously to creatinine, which is eliminated primarily by the kidneys. The SLC6A8 creatine transporter supports creatine uptake into cells; pathogenic variants can cause cerebral creatine deficiency syndromes with neurological manifestations.

Evidence for other applications is less certain. A small, uncontrolled pilot in people with AD reported increased brain creatine and improvements on some cognitive measures, but controlled studies are needed to determine whether creatine provides clinical benefit. A large trial found no benefit for slowing PD progression. Creatine combined with resistance training may support some muscle outcomes in older adults, and a small diabetes trial reported improved glycemic measures when creatine was combined with exercise. These findings do not establish creatine as a treatment or as a means of preventing age-related chronic disease. Antitumor findings are preclinical, and observational dietary data do not show that creatine supplements prevent cancer in people. Evidence that carbohydrate, fenugreek, and ashwagandha, supplements reliably increase creatine's effectiveness is also limited. Since oxidative stress generated during exercise can damage creatine transporter protein that can prevent entry of creatine into the cells, co-administration of creatine with antioxidants may prevent this effect of oxidative stress.

DECLARATION

Conflict of interest: The author is Chief Scientific Officer of Engage Global, Inc., a company that sells nutritional products to consumers.

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