A historical approach to creatine supplementation research over the last decades: From athletes to everyone

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A historical approach to creatine supplementation research over the last decades: From athletes to everyone

Uma abordagem histórica da pesquisa sobre suplementação de creatina nas últimas décadas: de atletas para todas as pessoas.

Un enfoque histórico de la investigación sobre la suplementación con creatina en las últimas décadas: desde los atletas hasta todos los públicos.

Short title: History of creatine supplementation research

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ABSTRACT

Despite being widely studied for decades, creatine supplementation still seems to hold many "secrets" and possible as-yet-unknown benefits can be revealed. Historically recognized as a supplement primarily for athletes, research conducted over time has revealed that, in addition to enhancing sports performance, it can improve the general population's quality of life and health. This narrative review aims to show some aspects of creatine supplementation, presenting the main findings that contribute to the current understanding of creatine supplementation for athletes and for both healthy and diseased children and older adults.

Keywords: creatine, nutritional supplement, exercise, health, treatment

RESUMO

Apesar de ser amplamente estudada há décadas, a suplementação de creatina ainda parece guardar muitos "segredos" e possíveis benefícios ainda desconhecidos podem ser revelados. Historicamente reconhecida como um suplemento principalmente para atletas, pesquisas realizadas ao longo do tempo revelaram que, além de melhorar o desempenho esportivo, ela pode melhorar a qualidade de vida e a saúde da população em geral. Esta revisão narrativa tem como objetivo mostrar alguns aspectos da suplementação de creatina, apresentando as principais descobertas que contribuem para a compreensão atual da suplementação de creatina para atletas e para crianças e idosos, tanto saudáveis quanto com doenças.

Palavras-chave: creatina, suplemento nutricional, exercício, saúde, tratamento

RESUMEN

Apesar de haber sido ampliamente estudiada durante décadas, la suplementación con creatina aún guarda muchos "secretos" y posibles beneficios aún desconocidos.

Históricamente reconocida como un suplemento principalmente para atletas, la investigación realizada a lo largo del tiempo ha revelado que, además de mejorar el rendimiento deportivo, puede mejorar la calidad de vida y la salud de la población general. Esta revisión narrativa tiene como objetivo mostrar algunos aspectos de la suplementación con creatina, presentando los principales hallazgos que contribuyen a la comprensión actual de la suplementación con creatina para atletas y para niños y adultos mayores, tanto sanos como con alguna enfermedad.

Palabras clave: creatina, suplemento nutricional, ejercicio, salud, tratamiento

Abbreviation:

ADP – Adenosine diphosphate

AGAT - Arginine:glycine amidinotransferase

Akt – Protein kinase B (also called PKB) is a serine/threonine kinase

AMPK - Adenosine monophosphate-activated protein kinase

Arg – Arginine

ATP – Adenosine triphosphate

BB-CK – CK brain-specific isoform

CK – Creatine kinase

CNS – Central nervous system

Cr – Creatine

CrP – Phosphocreatine

CrT – Creatine Transporter

GAA – Guinidinoacetate

GAMT - S-adenosylmethionine:guanidinoacetate methyltransferase

Gly – Glycine

IOC – International Olympic Committee

ISSN – International Society of Sports Nutrition

mTBI – Mild traumatic brain injury

PKB - Protein kinase B (also called Akt) a serine/threonine kinase

ROS – Reactive oxygen species

INTRODUCTION

Creatine is one of the most well-studied dietary supplements. Searching for the term “creatine supplementation” on PubMed.gov (up to March 26, 2026) returned a total of 3259 abstracts, exceeding the number of results for the term “caffeine supplementation”, with 1000 abstracts, and “whey protein supplementation”, with 1417 abstracts. Despite the extensive scientific literature, considerable debate remains, particularly among exercise and fitness professionals, regarding the safety of creatine supplementation. The safety concerns appear to be associated with anecdotal reports (Kreider et al, 2017; Rawson, 2018) and/or misinformation. From this perspective, creatine supplementation is widely used by athletes and non-athletes to improve performance, and, given the large number of potential customers, products containing creatine are abundantly available on the market. Nevertheless, recent studies have raised promising perspectives, hypothesizing that creatine supplementation could help to improve aged and/or injured brain health.

DISCUSSION

Creatine

Creatine (Cr) is a non-proteinogenic amino acid derivative, produced in the human liver, kidneys, and pancreas, in addition to being available in animal foods (Wyss and Kaddurah-Daouk, 2000; Ellery et al 2016; Alraddadi et al, 2018; Antonio et al, 2021). In 1832, Michel Eugène Chevreul identified creatine as a natural component present in skeletal muscle, and about 80 years later it began to be investigated as a dietary supplement (Ostojic, 2021).

Regarding its biological function, creatine plays a critical role in metabolism, being a metabolic intermediate for energy transfer. As shown in figure 1, it facilitates ATP resynthesis, depending only on one enzyme (Creatine Kinase - CK) that catalyzes very quickly the ADP phosphorylation, which explains creatine’s importance in tissues with high fluctuations in energy demand. This is why it is abundant in organs such as skeletal muscle and the brain, two of the tissues with the highest creatine concentrations.

Indeed, about 95% of the human body's creatine stores are located in skeletal muscle and the remaining 5% in the brain, liver, kidneys, and testes (muscle or brain maintain a total cellular Cr pool of up to 30–40 mM) (Wyss and Kaddurah-Daouk, 2000; Rackayova et al, 2017). The guanidino compounds creatine (Cr) and phosphocreatine (CrP) belong to the most abundant cellular metabolites in mammals including humans, with about 120 g present in a 70 kg adult male, and the rate of creatine loss is estimated to be ∼1.7% of the total body pool per day (Brosnan et al, 2013; Persky et al, 2003). Therefore, to compensate for this daily loss, the daily requirement is about 2 g of creatine, while half of this daily requirement can be synthesized endogenously, the remaining amount must be obtained through the diet (Alraddadi et al 2018; Rackayova et al, 2017; Candow et al,2021).

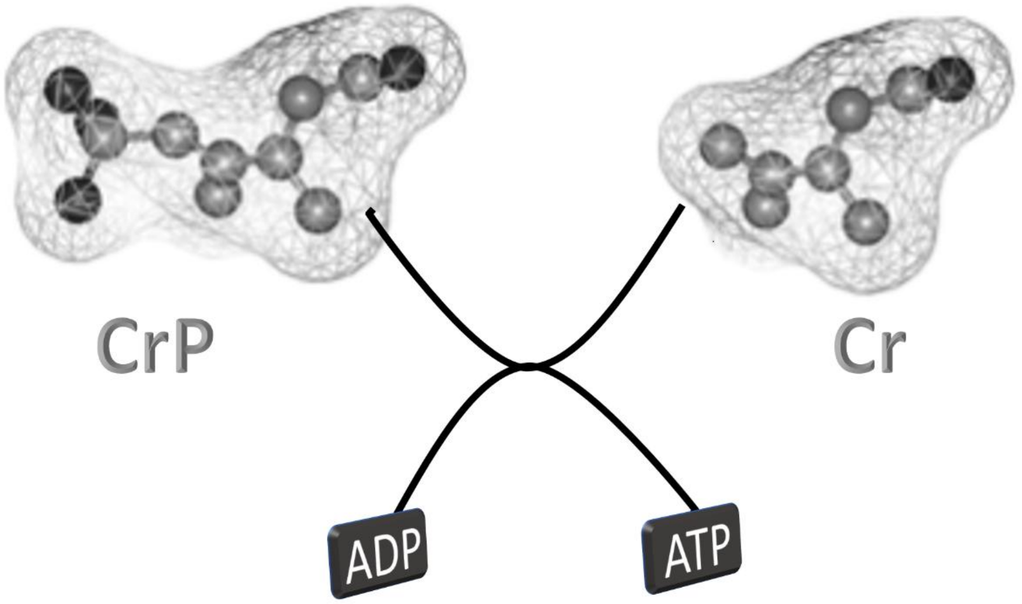

Figure 1 – Creatine's energy buffer function. Creatine kinase (CK) is the enzyme that catalyzes the reversible chemical reaction of transferring a phosphate group from phosphocreatine (CrP) to adenosine diphosphate (ADP), resulting in adenosine triphosphate (ATP) and free creatine (Cr).

Creatine as a supplement

Creatine supplementation is usually administered in two ways: loading or maintenance (see figure 2). The loading phase seeks to rapidly saturate muscle cells with creatine/phosphocreatine with doses of ~3.0 g.kg^{-1}.day^{-1}, commonly divided into 4 equal doses. This type of supplementation is suggested between 3 to 7 days. The maintenance phase typically consists of a single daily dose of ~0.3 g.kg^{-1}.day^{-1}, which may last for more than 14 days (usually studies show 28 days) (Kreider et al, 2017; Rawson, 2018; Maughan et al, 2018).

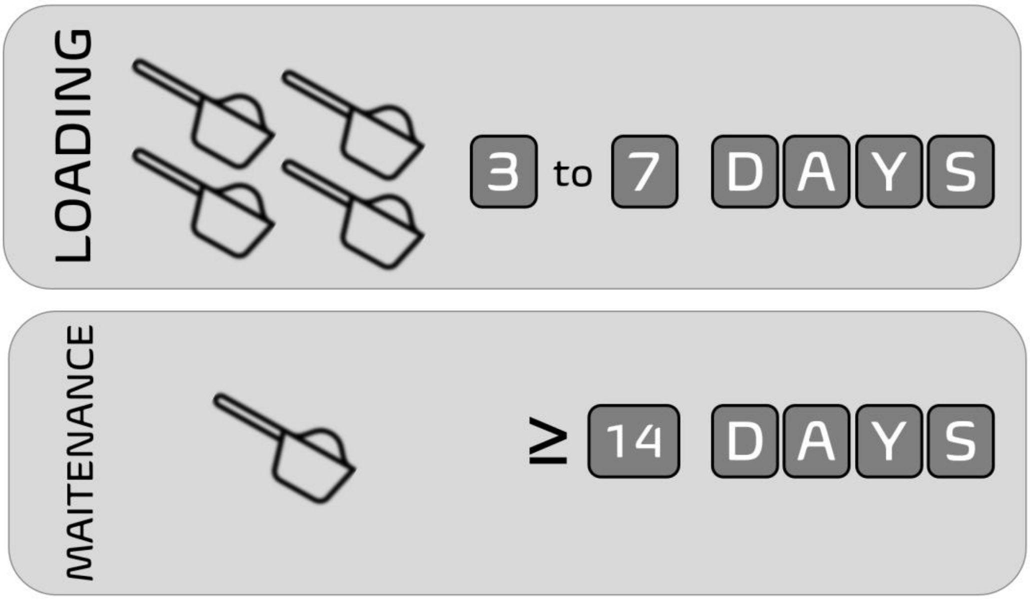

Figure 2 – Two main forms of creatine supplementation are described (they are not exclusive). In the upper part of the image, ~3.0g of creatine per kg/body mass, provided in 4 daily doses for 3 to 7 days (loading). In the bottom, maintenance approach, ~0.3 g of creatine is taken in a single daily dose for periods equal to or greater than 14 days (usually 28). Athletes in particular tend to use a combination of the two strategies, starting with the loading dose followed by maintenance. All image and text rights belong to (Machado, 2022).

We can divide creatine supplementation broadly into 3 modes: meat (beef, chicken, fish, etc.), dissolved in liquid, and solid (lozenge). The form diluted in water is undoubtedly the fastest way to absorb the ingested creatine. On the other hand, the intake of an equivalent amount of creatine from meat was associated with a delay in achieving the peak plasma concentration, but it sustained near-peak concentration for a longer period (Harris et al, 2022). Creatine absorption from lozenges tends to behave similarly to the meat absorption curves, except for the duration of the blood peak, which is shorter than others.

Excess supplemental creatine (i.e., the part not taken up by the tissues), is excreted in the urine (Wyss and Kaddurah-Daouk, 2000; Franz et al, 2021). It is described that the main factor determining the magnitude of increase in muscle creatine storage after supplementation is the baseline (i.e., the initial or the immediate pre-supplementation) muscle creatine storage, thus, low baseline muscle creatine storage tends to exhibit greater increases when compared to those with higher baseline values (Maughan et al, 2018; Antonio et al, 2021).

Muscle

Since this is a widely studied topic, with well-established recommendations IOC (Maughan et al, 2018) and ISSN (Kreider at al, 2017), add to the excellent work done by Wyss and Kadourah-Daouk (2000), here we will focus less on the topic of creatine supplementation and muscle-related issues.

The muscle bioavailability of creatine and phosphocreatine is increased by 15-40% after creatine monohydrate acute (loading) and chronic (maintenance) supplementation (Kreider at al, 2017; Maughan et al, 2018). Creatine as an ergogenic aid has been shown to augment body and muscle mass, enhance strength and improve the quality of high-intensity and intermittent training (Dos Santos et al, 2021). These effects were age-independent and have been observed in adolescents (Machado, 2022; Ostojic, 2004), younger adults (Almeida et al, 2020), and older individuals (Candow et al, 2019).

Creatine supplementation increases body mass, lean tissue mass, and upper and lower body muscle strength when concurrent with resistance training in older adults, but the potential mechanisms by which creatine exerts these positive effects remain incompletely understood and are being evaluated extensively by several research groups around the world (Chilibeck et al, 2017).

While the exact mechanisms remain to be fully established, evidence suggests that increases in intramuscular phosphocreatine stores following creatine (Cr) supplementation may enhance actin–myosin cross-bridge cycling (Marshal et al., 2022).

More pronounced adaptations appear to occur in older adults compared with younger individuals. Older individuals are reported to have lower baseline phosphocreatine stores than younger individuals, which may lead to greater strength adaptations following Cr supplementation. The literature consistently demonstrates the ability of creatine supplementation to elevate the phosphocreatine pool, thereby increasing the capacity to perform physical tasks due to enhanced energy resynthesis and subsequent greater gains in muscle strength. These effects may be explained by a faster detachment of the actin–myosin cross-bridge, which increases the capacity for force generation (Dos Santos et al., 2021).

Muscle-induced microdamage generates a mechanism called “repeated bout effect” (Veggi et al, 2013; Ferreira et al, 2012). Creatine supplementation provides an additive response on blunting exercise-induced muscle damage following a repeated bout of resistance exercise (Veggi et al, 2013). The mechanism by which creatine augments the repeated bout effect is unknown but is likely due to a combination of creatine’s multifaceted functions (Veggi et al, 2013).

Brain and Cognition

While muscle is exclusively dependent on exogenous and endogenous creatine as described (Wyss and Kaddurah-Daouk, 2000; Persky et al, 2003), the brain can synthesize creatine through the enzymatic machinery for endogenous creatine synthesis. In addition, creatine transporters are found in the blood-brain barrier, neurons and oligodendrocytes (Dolan et al, 2019; Ostojic and Forbes, 2021). However, there is evidence that brain creatine concentration can be increased via other sources (Dolan et al, 2019; Ostojic and Forbes, 2021) (see figure 3). Furthermore, brain creatine appears not to be influenced by habitual food intake, as a similar amount of brain CrP is found among vegetarians and omnivores (Ostojic and Forbes, 2021; Goldman et al, 2022).

Although most of the body's creatine is stored in skeletal muscle, the brain, a very active organ, is also dependent on the phospho-creatine system, as it accounts for up to 20% of the body's total energy expenditure. Creatine kinase is also expressed in a brain-specific isoform (BB-CK), which reinforces the relevance of this system in providing energy to the central nervous system (CNS) (Rackayova et al, 2017; Avgerinos et al, 2018; Borchio et al, 2020; Merege-Filho et al, 2017). Thus, it has been suggested that cognitive processing may also be affected by creatine metabolism. As the Cr/CrP system facilitates ATP homeostasis during periods of rapid or altered brain ATP turnover, which occurs during complex cognitive tasks, hypoxia, sleep deprivation, and some neurological conditions, creatine concentration may interfere with cognitive function (Ostojic and Forbes, 2021; Borchio et al, 2020; Merege-Filho et al, 2017; Roschel et al, 2021). The brain can synthesize creatine and it is not fully understood how much it depends on endogenous production from other organs or exogenous dietary sources (Merege-Filho et al, 2017).

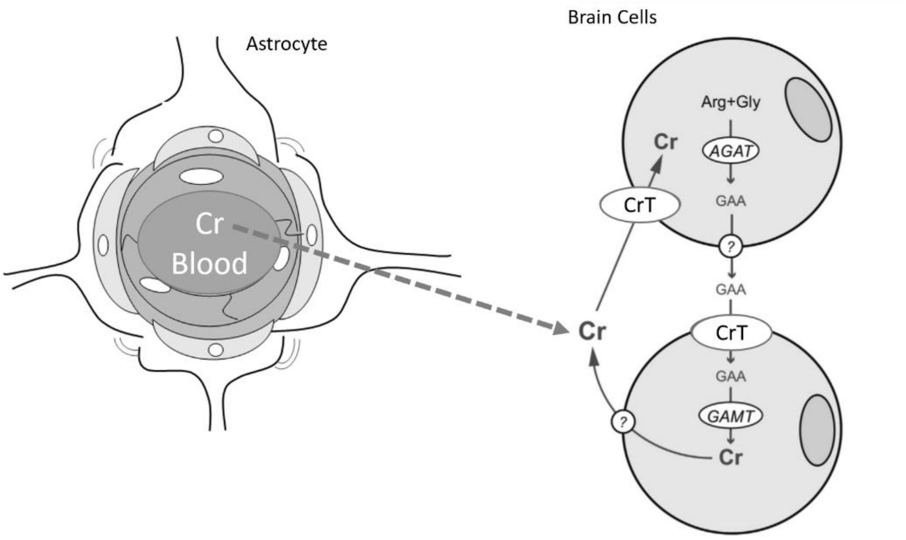

Figure 3 – The creatine used by brain cells is mostly produced by the brain cells themselves. It is a mechanism that is still being studied, but evidence shows that the process is not entirely carried out in the same cell. The blood-brain barrier is not very permeable to creatine, making it difficult for creatine produced in the kidneys/liver/pancreas or ingested in food to reach the brain cells, this transport is carried out via astrocytes.

Previous studies have shown that the brain concentration of creatine decreases with age, but it is still not known exactly why, despite some rising hypotheses suggesting it could be a product of the decreased physical activity, and not aging per se. Curiously, brain creatine may also decrease with age, but age-related decreases in brain creatine could result from reduced brain activity or disease (Avgerinos et al, 2018; Dolan et al, 2019; Ostojic and Forbes, 2021). Higher resting creatine levels have been proven to enhance performance in cognitive tasks such as recognition memory. It is suggested that this reduction in the Cr/CrP concentration may be part of the mechanism that leads to the age-associated cognitive capacity decline (Avgerinos eta al, 2018).

The effects of creatine supplementation on brain function appear to be larger under stressful conditions that lead to acute (e.g., mental fatigue, exhaustive exercise) or chronic (e.g., aging, depression, post-traumatic stress disorder) depletion of brain creatine, whereas no or minimal effect is shown in healthy individuals under unstressed conditions (Rawson and Venezia, 2012).

The exact circumstances and populations in which brain creatine is depleted remain to be determined by science, as these are potential targets to benefit from creatine supplementation. Although there appears to be a solid mechanistic basis in animals for creatine supplementation to mitigate deleterious effects or accelerate recovery from mild traumatic brain injury (mTBI), little data is yet available on this protective effect in humans (Dolan et al, 2019).

Borchio et al (2020) found significant improvement in some cognition indicators in mountain bikers supplemented with creatine and evaluated immediately after a strenuous ride. Athletes supplemented with creatine were faster and more successful in tests than athletes in the control group. Supplementation took place for 5 days before the test, with a dosage of 20 g.day^{-1}. These results do not support Rawson's review (2018) where youth supplemented with creatine had no cognitive benefit (Merege-Filho et al, 2017). Despite being very promising, the effects of creatine supplementation on cognition are still under investigation by the scientific community (Machado, 2024; 2025a; 2025b).

Health and disease

Currently, creatine supplementation has been suggested and applied as a treatment for several diseases. Parkinson’s disease, Alzheimer’s disease, diabetes mellitus, senile dementia, and sarcopenic obesity, among other diseases, have shown better prognosis when creatine supplementation is used as an adjunct (Dolan et al, 2019; Roschel et al 2021; Solis et al, 2021; Gualano et al, 2012; Machado, 2022; Tran et al, 2021; Mert et al, 2017). Support for respiratory diseases, intradialytic patients, and even COVID19 recovery is possibly positively affected by creatine supplementation when combined with conventional treatments (Ostojic, 2020; Wallimann et al, 2017; van der Veen et al, 2021).

Preclinical animal studies show potential benefits of creatine supplementation during pregnancy. Animal models and experimental designs were conducted trying to reproduce the metabolism of the creatine/phosphocreatine system in human pregnancy, showing results that allow a positive perspective in the analyzed context (Dickinson et al, 2014). Combining ergogenic results with potentially disease-reducing processes that can occur during a woman's reproductive years, it is necessary to understand whether creatine supplementation is safe for this population. The results have been promising; however, they need to be reproduced and expanded until they can be applied to clinical practice (Ellery et al, 2016; de Guingand et al, 2020).

Alternative mechanisms for Cr action have already been proposed. For example, evidence shows that the mitochondrial isoform of CK can mediate anti-oxidative or anti-apoptotic effects. Efficient maintenance of local cycling of energy phosphates inhibits reactive oxygen species (ROS) production in mitochondria and the pro-apoptotic permeability transition (Marshall et al, 2022). There is also evidence showing Creatine exerting direct antioxidant effects, by activating signaling pathways such as Akt/PKB or AMPK (Leite et al, 2021), inducing increased expression of muscle transcription factors and enzymes to defend against oxidative stress (Tokarska-Schlattner et al, 2012; Liu et al, 2021).

Even though the antioxidant, transductional and transcriptional mechanisms are not sufficient for in vivo situations, mechanisms involving molecular interaction between CrP with membrane phospholipids are also proposed (Tokarska-Schlattner et al, 2012). Amphipathic binding of phosphocreatine to phospholipids produces increased membrane stability, possibly affecting additional membrane-based processes like ion homeostasis and cell signaling. Thus, the suggested mechanism where CrP interacts with membranes and increases membrane packing gain relevance due to its plausibility (Tokarska-Schlattner et al, 2012; Liu et al, 2021).

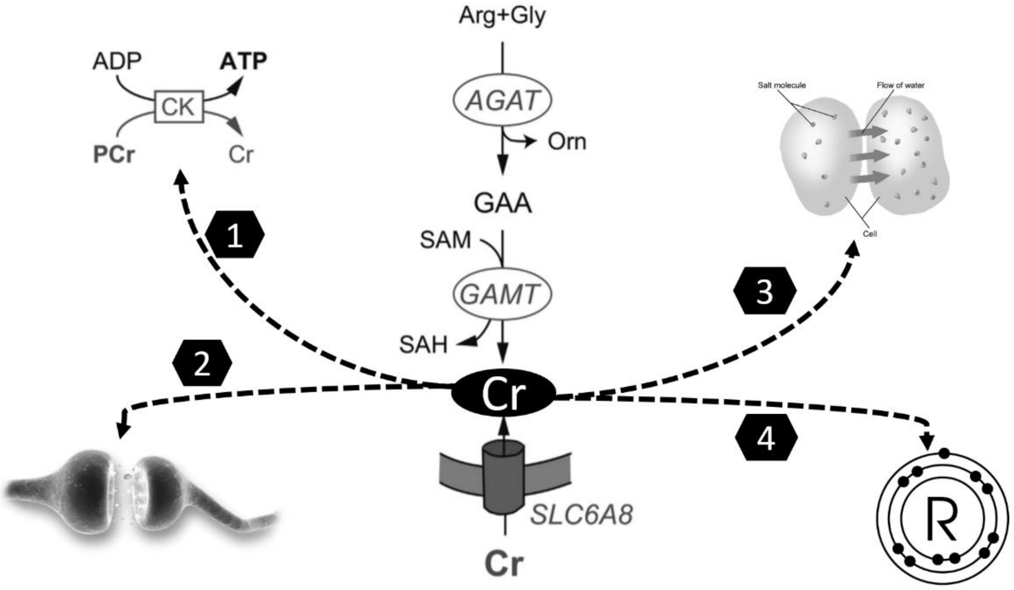

Figure 4 - The mechanisms by which the Cr/CrP/CK system protects brain cells are still unclear, but they seem to pass through at least 4 hypotheses: [1] energetic support maintaining the capacity of neurons and glia to function properly; [2] creatine can function as a neurotransmitter, favoring several cognitive functions; [3] as an osmotic agent, creatine contributes to cell balance; [4] the reaction catalyzed by CK and phosphocreatine/creatine itself can act as antioxidant agents preventing membrane degradation and apoptotic signaling.

Safety/Adverse Outcomes

The safety of creatine monohydrate supplementation has been well investigated

(Rawson, 2018; Jagim et al, 2018; Antonio et al, 2021; Machado et al, 2022; Almeida et al, 2022). The main concerns about the safety of creatine supplementation involve: impaired renal function, muscle dysfunction, or impaired thermoregulation. Based on available clinical trial data, there is no evidence suggesting that creatine supplementation at recommended doses impairs renal, muscular, or thermoregulation function (Rawson, 2018; Jagim et al, 2018; Antonio et al, 2021; Almeida et al, 2022). Instead of adverse outcomes, available data indicate that creatine supplementation, at recommended doses, may enhance muscle function (e.g., decreased muscle damage and inflammation following intense exercise (Machado et al, 2009; Veggi et al, 2013; Almeida et al, 2020) and thermoregulatory response to exercise (Lopez et al, 2009). Additionally, Guingnard et al. (2020) showed in females that mortality and serious adverse events should not be associated with Cr supplementation. Nor does the use of creatine supplementation increase the risk of total adverse outcomes, weight gain, or renal and hepatic complications in females (Ellery et al, 2016; Guingnard et al, 2020).

CONCLUSION

Despite being widely studied for decades, creatine supplementation still seems to hold many "secrets" and possible as-yet-unknown benefits can be revealed. A historical approach allows us to identify, beyond a promising ergogenic supplement, a therapeutic target to be used as an adjunct to treat several diseases, such as Parkinson's, Alzheimer's, Diabetes Mellitus, Senile Dementia, Sarcopenic Obesity, among other diseases, as well as recovery after COVID-19, highlighting the contemporary relevance of this “old” supplement.

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Authors’ contributions

Conceptualization; M.M. manuscript writing; M.M. manuscript revision: M.M. M.M. has read and approved the published version of the manuscript.

Declaration of Conflicting Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical Approval and Informed Consent

Ethical approval and informed consent were not required for this study, as it did not involve human participants or animal subjects.

Data Availability Statement

No datasets were generated or analyzed during the current study, and therefore data sharing is not applicable.

Consent for publication

Not applicable. This manuscript does not include data from individual persons (including individual details, images, or videos).

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