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A Comprehensive Review of Creatine Supplementation: From Foundational Bioenergetics to Evolving Therapeutic Applications and Clinical Safety

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Abstract

Creatine is a naturally occurring nitrogenous compound that plays a central role in cellular energy metabolism by facilitating rapid ATP resynthesis in tissues with high energetic demands, notably skeletal muscle and the brain. Although best known for enhancing exercise performance, contemporary evidence points to broader clinical potential across neurological conditions, muscle-wasting disorders, chronic diseases, and age-related loss of muscle mass. Supplementation increases creatine availability in muscle and brain, thereby sustaining energy flux, limiting oxidative stress, and supporting recovery, plasticity, and tissue repair. Populations with lower baseline stores, such as children, older adults, women, and individuals following vegan diets, may derive significant benefits. Importantly, creatine has been investigated extensively and demonstrates a strong safety profile, with no consistent evidence of kidney injury or serious adverse effects in healthy individuals or medically supervised clinical cohorts. Taken together, creatine should be considered not merely a sports supplement but a safe, versatile adjunct with relevance to health and function across the lifespan.

Keywords: creatine; creatine supplementation; creatine safety

1. Introduction

Creatine (Cr) is a ubiquitous, non-proteinogenic amino acid derivative fundamental to rapid energy provision in muscle and brain via the phosphocreatine–creatine kinase system. Approximately 50% of total body creatine is synthesized endogenously, with the remainder obtained through the diet, predominantly from meat and fish. The daily requirement is typically estimated at 2–4 g, depending on muscle mass and overall level of physical activity. While creatine is widely recognized and extensively studied as an ergogenic aid, its physiological significance extends beyond athletic performance. The objective of this review is to move past the conventional sports context and appraise additional applications of creatine. We first summarize its bioenergetic mechanisms as a foundation for evaluating putative therapeutic roles in both clinical and non-athletic populations. In parallel, we provide a critical appraisal of safety, directly addressing common misconceptions and considering how differing physiological states may modify efficacy and risk.

2. Methodology

This review synthesizes literature identified through PubMed, Google Scholar, and ScienceDirect. The search was conducted between June and August 2025. Medical Subject Headings (MeSH) and keyword strategies were used and articles were limited to English-language publications only. Study identification and screening are depicted in Figure 1. The literature review included studies published between 2011 and 2025, with particular emphasis on the most recent decade to ensure relevance and timeliness. All studies selected for inclusion were evaluated for methodological quality and relevance and were approved by all co-authors.

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only

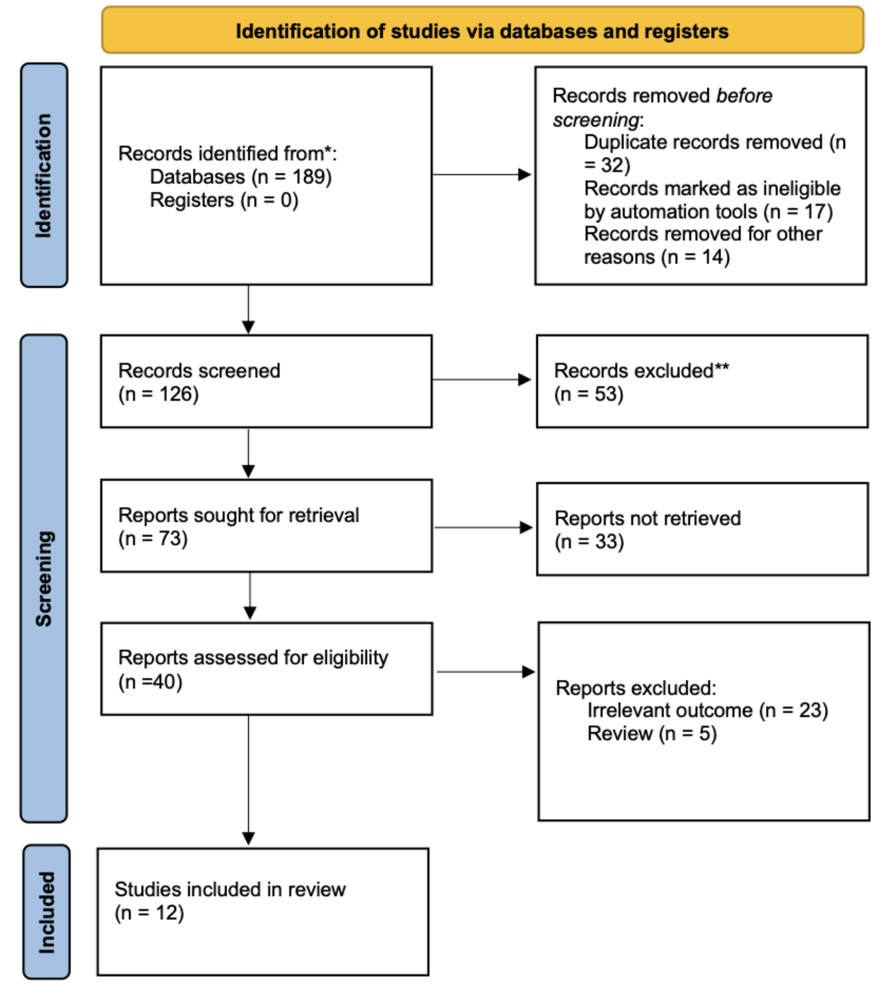

Fig 1: PRISMA flow diagram of selected studies

3. Creatine Kinase/Phosphocreatine System: Fundamental Mechanisms of Cellular Bioenergetics

Creatine kinase/phosphocreatine (CK/PCr) system is physiologically crucial for existence and is a significant evolutionary advantage for cell survival, growth and differentiation (Bonilla et al., 2021). The system provides rapid, localized and temporal energy supplementation for functions heavily dependent on mechanical and metabolic energy (Bonilla et al., 2021). The foundation for this process is the reversible enzymatic reaction that transfers a high-energy phosphate group from phosphocreatine (PCr) to adenosine diphosphate (ADP), with the result of rapidly replenishing adenosine triphosphate (ATP) (Kreider et al., 2017). This rapid re-phosphorylation is especially significant under conditions of short-duration, high-intensity exercise, or for repeated sets of high-intensity exercise with periods of short recovery when the demand for ATP turnover is greater than the rate of aerobic metabolism (Kreider et al., 2017).

The transport of creatine into the target tissues, such as muscle and brain, is fascilitated by a specific sodium- and chloride-dependent transporter known as the creatine transporter (CRT) (Bonilla et al., 2021). Creatine supplementation elevates intramuscular and cerebral creatine and phosphocreatine concentrations by 10-40% in adults, thus enhancing the cellular capacity to provide energy rapidly and buffer fluctuations in energy demand (Kreider et al., 2025). Uptake can vary by age, with increased rises observed in elderly individuals compared to children and adult omnivores (Kreider et al., 2025).

Beyond its role in bioenergetics, creatine also exerts significant cell-mediated effects. It has been shown to reduce the generation of reactive oxygen species (ROS) and muscle catabolism, while also inhibiting inflammatory processes (Bonilla et al., 2021; Kreider et al., 2017). Evidence also suggests creatine enhances gene expression and satellite cell activation, mechanisms involved in hypertophic responses and muscle growth. (Kreider et al., 2017).

The underlying bioenergetic buffering function of creatine provides a paradigm for the convergence of its potential therapeutic advantages. Metabolic stress-tolerating systems, whether from disease, trauma or prolonged physiological injury, appear to demonstrate more effects (Bonilla et al. 2021). Several diseases have been linked with perturbations of creatine metabolism, where supplementation might be compensatory (Kreider et al., 2017). This reframes creatine not just as an ergogenic aid but as a homeostatic regulator, with profound implications for conditions like traumatic brain injury and muscle atrophy disorders.

4. Expanding Therapeutic and Clinical Applications

Neurological Health and Cognitive Function

The neuroprotective effects of creatine are attributed to its role in maintaining ATP homeostasis in the brain which represents about 20% of the body's total energy demand (Bonilla et al., 2021). Such protection is particularly advantageous under conditions of rapid brain ATP turnover, including complex cognitive activity, hypoxia, sleep deprivation or neurological diseases (Bonilla et al., 2021). Additional antioxidant function might contribute to therapeutic in neurodegenerative disorders (Bonilla et al., 2021). Clinical data demonstrate benefits in creatine-deficient syndromes where supplementation has been shown to partly reverse developmental and cognitive disorders (Bonilla et al., 2021). In healthy individuals systematic review reported subtle yet significant improvements in working memory, particularly for tasks such as the Backward Digit Span test (Xu, 2024). Similarly, recent randomized controlled trial demonstrated enhancements in cognitive performance on specific tasks following supplementation (Sandkühler et al., 2023). Creatine also shows promise in mild traumatic brain injury (mTBI) with evidence of improved cognitive recovery and reduced headaches frequency (Bonilla et al., 2021). Neurodegenerative diseases such as Parkinson's, Huntington's, and Alzheimer's may also benefit, though findings remain mixed (Kreider et al., 2017).

Skeletal Muscle Disorders and Myopathies

Beyond athletic populations, creatine supplementation has also been shown to benefit patients with muscle disorders. A meta-analysis reported improvements in strength and lean mass in individuals with dystrophies with the strongest effects observed in dystrophinopathies and myotonic dystrophy type 2 (Kreider et al., 2017). Mechanism include reducing necrosis, protein degradation and ROS production (Bonilla et al., 2021).

However, therapeutic efficacy is not consistent across all myopathies. Creatine supplementation shows limited clinical response in myotonic dystrophy type 1 and facioscapulohumeral dystrophy, and may even aggravate symptoms in McArdle disease, where increased muscle pain has been reported.

Chronic Disease Management and Atrophic Conditions

Creatine may be helpful in treating chronic diseases and reducing wasting syndrome. While it is recommended to be careful with patients who have existing kidney disease (Kim et al. , 2011; Longobardi et al. , 2023), recent research indicates that supplementation may be safe and advantageous when observed under clinical supervision. For instance, extended use of supplements among patients undergoing hemodialysis led to enhancements in fat-free mass, skeletal muscle mass index, muscle strength, and overall quality of life (Marini et al. , 2024). Creatine is currently under examination for its potential effects on sarcopenia, osteoporosis, and type 2 diabetes (Kreider et al. , 2017).

5. Benefits Across the Lifespan and in Specific Populations

Children and Adolescents

Despite common concerns, creatine has a solid safety record throughout life, including for children (Jagim and Kerksick, 2021; Kreider et al. , 2025). Research indicates no connection between the use of creatine and negative health effects, disordered eating patterns, or increased risk of substance abuse (Jagim and Kerksick, 2021). Rather, users are often individuals who prioritize health and are in search of performance or wellness advantages (Jagim and Kerksick, 2021).

In clinical settings, creatine has shown advantages in pediatric conditions like acute lymphoblastic leukemia and Duchenne muscular dystrophy (Jagim and Kerksick, 2021). Limiting its use among young people may therefore have negative public health implications.

The Elderly

Creatine shows potential as a treatment option for sarcopenia and the decrease in muscle mass and function that occurs with aging. By promoting pathways that build, prevent breakdown, and repair, it aids in maintaining muscle mass and improving ATP regeneration (Marini et al. , 2024). Research also indicates its importance in reducing the risk of osteoporosis and type 2 diabetes (Kreider et al. , 2017).

Women and Vegans

Women or vegans may find supplementation especially beneficial. Women generally produce less creatine naturally and consume less through their diet. In contrast, vegans have lower creatine levels from the beginning because they do not eat animal products (Gutiérrez-Hellín et al. , 2024). Supplements taken by these groups result in notable rises in intramuscular creatine, and there is some indication that women might also face less fatigue during specific phases of their menstrual cycles (Gutiérrez-Hellín et al. , 2024).

6. Clinical Safety Profile and Considerations

Renal Function: Distinguishing Biomarkers from Pathology

The kidneys' safety is a major issue. Creatine naturally converts to creatinine, which raises serum creatinine levels without indicating renal dysfunction (Longobardi et al., 2023). Gold-standard assessments of glomerular filtration rate (e.g., 51Cr-EDTA clearance) and extensive research involving athletes and older individuals demonstrate that there are no negative effects on the kidneys, even with the consumption of high-protein diets or long-term use (Lugaresi et al. , 2013; Kim et al. , 2011).

Systematic Analysis of Adverse Events

Extensive studies of negative event reports indicate that creatine is very safe. Such reports are quite uncommon and are usually complicated by the intake of additional substances (Galvan et al. , 2016). Most claims of side effects are not supported by controlled clinical evidence.

Safety in Specific Populations and Recommended Formulations

Creatine is considered safe for children, adults, and older individuals when used appropriately. Caution is advised in those with severe renal disease, who should undergo monitoring if supplementation is considered (Kim et al., 2011). Importantly, creatine monohydrate remains the most studied, safe, and cost-effective form (Kreider et al., 2017; Gutiérrez-Hellín et al., 2024). New methods should be handled carefully unless supported by research evidence (Kreider et al., 2017).

7. Practical Recommendations and Future Research Directions

The most practical approach to creatine supplementation involves taking 3–5 grams of creatine monohydrate daily on a consistent basis. This continuous regimen provides comparable effectiveness to loading strategies while minimizing the likelihood of gastrointestinal issues (Kreider et al., 2017).

Future investigations should focus on identifying the most effective strategies for enhancing brain creatine levels and improving cognitive performance (Bonilla et al., 2021). Moreover, larger-scale clinical trials are needed to verify the potential cognitive advantages of creatine (Xu, 2024; Sandkühler et al., 2023). Additional promising areas of study include the supplement's possible influence on immune function, inflammatory pathways, and cancer biology (Kreider et al., 2017).

8. Conclusion

Creatine is among the most thoroughly researched and scientifically supported nutritional supplements, with strong evidence confirming its safety and efficacy across different groups and settings (Kreider et al., 2017; Kreider et al., 2025). Its fundamental role as an energy buffer explains its wide-ranging benefits—from enhancing physical performance to serving as a therapeutic agent in various medical and aging-related contexts (Bonilla et al., 2021).

Concerns about potential renal risks are not supported by high-quality scientific data (Longobardi et al., 2023). Reported adverse effects are uncommon and generally not directly attributable to creatine use (Galvan et al., 2016). Among available forms, creatine monohydrate remains the most well-validated, safe, effective, and affordable option (Gutiérrez-Hellín et al., 2024).

Overall, creatine should be viewed not merely as an ergogenic supplement, but as a valuable therapeutic compound with applications across the human lifespan and in numerous clinical conditions.

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