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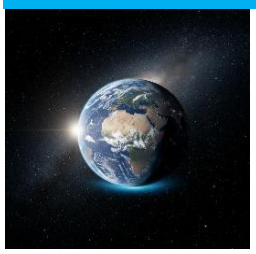

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Beyond Athletic Performance: The Emerging Role of Creatine Supplementation in Clinical Medicine — A Narrative Review

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ABSTRACT:

Introduction. Creatine monohydrate is among the most extensively researched dietary supplements, yet it remains widely perceived as a tool of athletic performance enhancement. Its fundamental role in cellular energy homeostasis across metabolically demanding tissues — including skeletal muscle, brain, and myocardium — suggests a broader clinical relevance that has not been systematically addressed in recent literature.

Materials and Methods. A narrative review was conducted using PubMed and Google Scholar, focusing on peer-reviewed original research, systematic reviews, meta-analyses, and position statements published up to April 2025. Search terms included combinations of "creatine," "creatine monohydrate," "phosphocreatine," and condition-specific terms covering skeletal muscle diseases, neurodegenerative disease, depression, sarcopenia, type 2 diabetes, cancer cachexia, traumatic brain injury, pregnancy, and renal safety. A total of 98 sources were included.

Conclusions. Creatine supplementation demonstrates well-established ergogenic efficacy in sport and clinically meaningful benefits in skeletal muscle diseases, sarcopenia, and cognitive ageing. Promising evidence supports its adjunctive role in depression and type 2 diabetes, while data in traumatic brain injury remain largely paediatric. Evidence in cancer cachexia is predominantly negative. The safety profile of creatine monohydrate is reassuring across age groups; the observed rise in serum creatinine represents a pharmacokinetic artefact. Pregnant women and patients with advanced chronic kidney disease require individualised assessment. Across clinical areas, mechanistic evidence is often compelling but large trials with standardised dosing and clinically meaningful endpoints remain scarce. Creatine is not only for athletes — its accessibility, tolerability, and growing clinical evidence base make it a strong candidate for broader integration into clinical practice.

Keywords: creatine, creatine monohydrate, clinical applications, neuroprotection, sarcopenia, muscle aging, cachexia, Diabetes Melitus type 2, chronic kidney disease, brain injury, depression, pregnancy, pediatric population, safety, narrative review, phosphocreatine

1. Introduction.

Creatine was first isolated in 1832 by the French chemist Michel Eugène Chevreul, yet it remained largely a biochemical curiosity for over a century. Its transition into sports science began in earnest in the late 1980s and early 1990s, when researchers at the Metabolic Research

Laboratory — most notably Roger Harris, Jonas Bergström, and Eric Hultman — demonstrated that oral creatine monohydrate supplementation significantly increases intramuscular creatine and phosphocreatine concentrations, with direct and measurable effects on high-intensity exercise performance [1]. Reports of creatine use among athletes at the 1992 Barcelona Olympic Games, where it was described in the popular press as a "secret weapon" of gold medallists, brought this finding to widespread public attention [1]. In the years that followed, creatine became the most commonly used ergogenic supplement in sport, valued primarily for its ability to improve strength, power output, and high-intensity exercise capacity [2].

The scientific landscape surrounding creatine has shifted considerably since those early years. Once regarded almost exclusively as a sports supplement, creatine is now increasingly recognised as a pleiotropic molecule with fundamental roles in cellular energy homeostasis across virtually every metabolically demanding tissue in the body [2,3]. An expanding body of research has begun to explore its potential in clinical medicine and healthy ageing, covering areas as diverse as neurodegenerative disease, depression, type 2 diabetes, sarcopenia, and cancer cachexia [2]. Concurrently, longstanding safety concerns — particularly regarding renal function — have been the subject of extensive investigation, with the accumulated evidence providing important clarifications for both clinicians and consumers [4,5].

The aim of this narrative review is to synthesise the available evidence on creatine supplementation across a range of contexts — from its biochemistry and mechanisms of action, through its established role in sport, to its emerging applications in clinical medicine and healthy ageing, alongside a discussion of its safety profile and relevant contraindications. In doing so, it addresses a question that the available evidence renders far from rhetorical: is creatine truly only for athletes?

2. Research materials and methods.

This study was conducted as a narrative review. Literature was identified through searches in PubMed and Google Scholar using keywords combinations of "creatine," "creatine monohydrate," "phosphocreatine," and condition-specific terms covering skeletal muscle diseases, neurodegenerative disease, depression, sarcopenia, type 2 diabetes, cancer cachexia, traumatic brain injury, pregnancy, and renal safety. Priority was given to publications from the last 10 years, including peer-reviewed original research, systematic reviews, meta-analyses, clinical guidelines and position statements. Studies were selected based on relevance, scientific quality, and applicability to clinical practice.

3. What is Creatine? Biochemistry and Physiology.

Creatine ($C_4H_9N_3O_2$) is a naturally occurring nitrogenous compound synthesised endogenously at a rate of approximately 1 g per day, primarily in the liver, kidneys, and pancreas, although the brain and testes are also capable of limited creatine production [3]. Its biosynthesis proceeds through two sequential enzymatic steps: first, an amidino group is transferred from L-arginine to L-glycine by the enzyme arginine:glycine amidinotransferase (AGAT), yielding guanidinoacetate (GAA); second, GAA is methylated by guanidinoacetate N-methyltransferase (GAMT) using S-adenosyl-L-methionine as a methyl donor, producing creatine [3]. The kidneys play a particularly critical role in the first of these steps via AGAT, and this synthetic capacity has been shown to decline progressively with advancing chronic kidney disease — a finding with clinical implications discussed in the context of safety and special populations [6]. Once synthesised, creatine is released into the bloodstream and taken up by target tissues via a sodium- and chloride-dependent creatine transporter (CRT1, encoded by SLC6A8) [3].

In addition to endogenous synthesis, creatine is obtained through diet. It is a carninutrient — a term reflecting the fact that it is available to adults almost exclusively through animal-derived foods, principally skeletal muscle meat and fish [7]. A typical omnivorous diet provides approximately 1–2 g of creatine per day, sufficient to maintain muscle creatine stores at roughly 60–80% of their maximum capacity [2,7]. Cooking reduces the creatine content of meat, as heat promotes its spontaneous conversion to creatinine — an effect that becomes more pronounced with prolonged cooking times and higher temperatures [7]. Individuals following vegetarian or vegan diets consume negligible amounts of dietary creatine, resulting in significantly lower baseline intramuscular and plasma creatine concentrations compared to omnivores [7].

The vast majority of the body's total creatine pool — approximately 95% — is stored in skeletal muscle, where it exists in two forms: roughly 60% as phosphocreatine (PCr) and the remainder as free creatine [2]. Significant creatine concentrations are also found in tissues with high and fluctuating energy demands, including cardiomyocytes, neurons, hepatocytes, and photoreceptor cells [3]. Within cells, creatine kinase catalyses the reversible phosphorylation of creatine by ATP to form phosphocreatine and ADP — a reaction that constitutes the biochemical basis of creatine's role in cellular bioenergetics [3]. The phosphocreatine stored in muscle represents the body's most immediately available energy reserve: during the first seconds of maximal effort, when ATP demand exceeds the capacity of oxidative metabolism, PCr rapidly donates its phosphate group to regenerate ATP from ADP, sustaining high-intensity muscle contractions before glycolytic and aerobic pathways can fully engage [2,3]. As both

skeletal muscle and the brain rank among the tissues with the highest creatine demands, individuals with lower baseline stores — including vegans and older adults — may show a proportionally greater response to supplementation in terms of both physical performance and cognitive function [3,7,8].

The final product of creatine catabolism is creatinine, formed through spontaneous, non-enzymatic, and irreversible degradation of creatine and phosphocreatine at a rate of approximately 2% of the total body pool per day [5]. Creatinine is freely filtered at the glomerulus and excreted in urine, and its serum concentration is widely used as a clinical surrogate of glomerular filtration rate [2,5]. This relationship carries an important practical implication: creatine supplementation, by expanding the total body creatine pool, inevitably raises creatinine production and serum concentration in proportion — a metabolic confound rather than a marker of renal injury, a distinction examined in detail in the section on renal safety [5].

4. Mechanisms of Action.

4.1. The ATP-Phosphocreatine System.

The primary mechanism of action of creatine is rooted in its role within the ATP-phosphocreatine (ATP-PCr) system — the most immediate energy pathway available to cells with high and fluctuating energy demands [9]. Within cells, creatine kinase (CK) catalyses the reversible transfer of a phosphate group from phosphocreatine (PCr) to adenosine diphosphate (ADP), regenerating adenosine triphosphate (ATP) within milliseconds [9,10]. This reaction constitutes the fastest mechanism of ATP resynthesis available to the cell, operating independently of oxygen and preceding the activation of glycolysis or oxidative phosphorylation [10]. The PCr pool thus functions as a spatial and temporal energy buffer — rapidly replenishing ATP at the site of demand while slower metabolic pathways engage [9,11].

A key feature of this system is its intracellular compartmentalisation. Different isoforms of creatine kinase are strategically positioned within the cell — in close proximity to mitochondria, where ATP synthesis occurs, and at sites of ATP consumption such as myofibrils and the cell membrane [3]. This creates the so-called phosphocreatine shuttle — an energy transfer system enabling rapid transport of phosphate equivalents across intracellular distances without requiring the diffusion of ATP itself [3,9]. This mechanism is particularly important in large cells or those with high and irregular energy demands, such as cardiomyocytes, neurons, and

type II muscle fibres. Approximately 60% of intramuscular creatine is stored in its phosphorylated form, providing a substantial but finite reservoir that is depleted within the first seconds of maximal-intensity effort [2,9]. The CK/PCr system also functions as a pH buffer — the dephosphorylation of PCr consumes free protons, slowing intracellular acidification during intense exercise and thereby delaying the onset of metabolic fatigue [3,11].

4.2. Role in ATP Resynthesis During Exercise.

During high-intensity exercise, the rate of ATP hydrolysis in skeletal muscle can exceed the capacity of oxidative phosphorylation by several orders of magnitude [10]. Under these conditions, the CK/PCr system becomes the dominant energy source, sustaining peak power output during the critical initial seconds of effort [9,10]. The relative contribution of PCr to total energy provision is greatest at the very onset of maximal effort and declines progressively as exercise duration increases, with glycolysis and oxidative phosphorylation assuming an increasingly dominant role [2,10]. As phosphocreatine concentration falls below a critical threshold, lactate production increases, intracellular pH declines, and muscular fatigue ensues. An important characteristic of the PCr system is its capacity for rapid resynthesis during recovery. Unlike glycogen, whose full replenishment requires many hours, the PCr pool is largely restored within 3–5 minutes of rest following exercise — a process tightly dependent on oxygen availability and mitochondrial efficiency [9,10]. This property makes the PCr system particularly relevant in interval and team sports, where an athlete repeatedly performs short maximal efforts with incomplete recovery. The higher the baseline PCr concentration and the more efficient its resynthesis, the longer high-intensity performance can be sustained across successive repetitions [10]. This relationship between PCr stores, their rate of resynthesis, and exercise capacity constitutes the physiological foundation for interest in creatine as an ergogenic supplement, addressed in detail in the following chapter.

4.3. Effects Beyond Skeletal Muscle: Brain and Heart.

While skeletal muscle contains approximately 95% of the body's creatine, the ATP-PCr system is functionally essential in all tissues with high energy demands — most notably the brain and heart [3,9]. In the central nervous system, creatine is present in synaptic vesicles and may directly influence cortical neuron communication, while also stimulating mitochondrial activity in hippocampal neurons [3,11]. Its neuroprotective potential is linked to oxidative stress modulation, anti-inflammatory effects, and support of neurodevelopment [3,11]. Recent

biochemical and electrophysiological evidence further suggests that creatine may function as an inhibitory neurotransmitter in the CNS — it has been detected in synaptic vesicles at concentrations exceeding those of acetylcholine and serotonin, and calcium-dependent release following neuronal stimulation has been demonstrated, though the evidence does not yet reach the level of proof established for classical neurotransmitters [12]. Beyond direct neuronal effects, creatine supplementation may indirectly support brain function through the muscle-brain axis — a signalling framework whereby skeletal muscle, functioning as an endocrine organ, releases myokines such as brain-derived neurotrophic factor (BDNF), irisin, and IGF-1 in response to contraction [8,11]. By enhancing exercise capacity and training volume, creatine may amplify myokine secretion, thereby promoting neuroplasticity, neurogenesis, and cognitive function [8,11].

In the heart, PCr plays an equally critical role. Cardiomyocytes rely on the CK/PCr system to maintain continuous ATP availability for myocardial contraction [2,9]. Under physiological conditions, the PCr-to-ATP ratio in cardiac muscle serves as a sensitive indicator of myocardial energy status, and its reduction is a hallmark of heart failure [9]. Dysregulation of creatine metabolism in the heart — including decreased creatine transporter expression and PCr depletion — contributes to impaired contractility and reduced cardiac output observed in failing hearts [2,9]. These findings position creatine not merely as a sports supplement, but as a molecule with fundamental roles in the energetic homeostasis of multiple organ systems [3,9].

5. Creatine in Sport.

5.1. Creatine and Muscle Strength and Mass.

Among all documented ergogenic effects of creatine, its impact on muscle strength and hypertrophy is the most extensively studied — creatine monohydrate is currently regarded as one of the few dietary supplements with unequivocally proven ergogenic efficacy [2,13]. Creatine supplementation combined with resistance training consistently increases maximal strength, power output, and the capacity to perform repeated high-intensity efforts [13]. The mechanisms underlying these effects extend beyond simply increasing the intracellular PCr pool, encompassing modulation of growth factors, satellite cells, protein kinetics, and muscle glycogen content, as well as effects on inflammation and oxidative stress which play an important role in training adaptation [14]. A meta-analysis by Burke et al. demonstrated that the combination of creatine supplementation and resistance training leads to a small but

statistically significant increase in muscle thickness in both the upper and lower extremities (0.10–0.16 cm), with the effect more pronounced in younger compared to older adults [14]. Subgroup analysis further revealed that effects are similar for flexors and extensors of both the upper and lower limbs, suggesting that creatine exerts a uniform influence on hypertrophy regardless of muscle group [14]. It should be noted that part of the observed variability in results may reflect the presence of so-called non-responders — individuals in whom supplementation does not meaningfully increase intramuscular creatine stores, estimated at approximately 20–30% of the population, which may be associated with high baseline creatine levels, a low proportion of type II fibres, or low fat-free mass [14].

A meta-analysis by Zhang et al. confirmed that creatine significantly improves muscle strength across the general population [15]. Subgroup analysis demonstrated that untrained individuals derive greater benefits than trained ones, and that low-to-moderate dose supplementation combined with high-intensity training yields superior outcomes compared to high-dose protocols [15]. A portion of observed lean body mass gains may reflect intracellular water retention rather than true hypertrophy [14,16]. Desai et al. demonstrated that a 7-day loading phase increased lean body mass — particularly in females — whereas a subsequent maintenance dose of 5 g/day did not produce additional lean mass gains compared to controls during a 12-week resistance training programme, which the authors attribute to dissipation of the short-term water retention effect following loading [16]. Given the considerable heterogeneity across available studies — encompassing varying dosing protocols, age groups, training status, and outcome measurement methods — formulating universal supplementation recommendations remains challenging [14,15,16]. The overall trend in the literature is nonetheless consistent: creatine supplementation combined with resistance training yields measurable benefits in strength and body composition in the majority of healthy physically active individuals [2,14,15].

5.2. Creatine and Exercise Performance and Fatigue.

Creatine exerts well-documented ergogenic effects in disciplines based on short-duration, high-intensity effort, including sprinting, weightlifting, and team sports [13]. Supplementation consistently increases maximal work output, power production, and the ability to sustain exercise intensity across multiple repetitions, as demonstrated in both elite athletes and recreationally active individuals [13,15]. These effects stem directly from the energy buffering mechanism described in the previous chapter — a larger PCr pool allows for longer

maintenance of peak intensity before the onset of metabolic fatigue [17]. Supplementation increases the total intramuscular PCr pool, thereby extending the duration over which maximal power can be maintained and — equally importantly — accelerating PCr resynthesis during recovery between high-intensity bouts [2,15,17]. This accelerated restoration of PCr stores is particularly valuable in interval and team sports, where an athlete repeatedly performs short maximal efforts with incomplete recovery [15,17]. Creatine has also been shown to enhance muscle glycogen resynthesis when co-ingested with carbohydrates, representing an additional benefit for athletes performing repeated high-intensity efforts [2,17].

The picture is more nuanced in endurance sports. Creatine does not increase maximal oxygen uptake nor improve time trial performance based solely on aerobic metabolism, and combining creatine with other common ergogenic agents such as caffeine or sodium bicarbonate does not produce additive performance benefits in endurance-trained individuals [17,18]. Its potential benefit in endurance contexts instead derives from increased anaerobic work capacity and attenuation of exercise-induced inflammation and oxidative stress [17,19]. In practice, creatine may be particularly useful in endurance disciplines requiring repeated surges in intensity — such as cycling, rowing, kayaking, and cross-country skiing — where the capacity to generate short bursts of high-intensity effort is a key performance determinant [17]. The body mass gain associated with supplementation may, however, offset potential benefits in disciplines where mass directly influences performance efficiency, such as long-distance running [15,17].

5.3. **Creatine and Post-Exercise Recovery.**

Growing evidence suggests that creatine supports post-exercise recovery through several complementary mechanisms. Supplementation attenuates muscle damage, reduces inflammatory markers, and accelerates recovery of force-production capacity following intense exercise [13]. Mechanistically, creatine may limit muscle damage through stabilisation of cell membranes, improved energy availability during the recovery phase, and modulation of intracellular inflammatory signalling [13,19]. The ISSN position stand on dietary antioxidants in sport classifies creatine monohydrate — at a dose of 0.1 g/kg/day for 5–10 weeks — as a supplement with a high level of evidence for performance enhancement with potential antioxidant and anti-inflammatory support, noting reductions in pro-inflammatory cytokines including TNF-α and PGE2 following exercise [19]. These antioxidant and anti-inflammatory properties are considered additive to creatine's primary ergogenic role rather than its defining characteristic [19]. Creatine has also been shown to accelerate muscle glycogen resynthesis

following glycogen-depleting exercise when co-ingested with carbohydrates, adding a further regenerative dimension particularly relevant for endurance and team sport athletes [13]. While techniques such as massage, hydrotherapy, and compression garments demonstrate efficacy primarily in reducing delayed-onset muscle soreness and perceived fatigue [20], creatine acts at a more fundamental level — attenuating the process of muscle damage and inflammation itself rather than merely alleviating its symptoms [13,19].

5.4. Dosing and Supplementation Protocols.

Two principal supplementation protocols are described in the literature. The loading protocol involves ingestion of 20 g/day divided into four 5 g servings for 5–7 days, followed by a maintenance phase of 3–5 g/day [2,13]. This approach allows rapid muscle creatine saturation within one week but may be associated with transient gastrointestinal discomfort and acute body mass gain due to water retention [2]. The constant dose protocol involves daily ingestion of 3–5 g without a loading phase, leading to a gradual increase in the PCr pool over 3–4 weeks and is better tolerated by most individuals [2,13]. Available data do not indicate a meaningful difference in long-term outcomes between the two protocols — the final level of muscle creatine saturation is comparable [2]. For most users, the constant dose protocol represents the preferable option due to its simplicity, better tolerability, and absence of abrupt changes in body mass [13,16].

5.5. Forms of Creatine.

Although numerous forms of creatine are commercially available, creatine monohydrate remains the gold standard — it is the most extensively researched form, characterised by high bioavailability, proven efficacy, and a well-established safety profile [2,21]. The vast majority of clinical evidence supporting the ergogenic and health-related effects of creatine derives from studies using this specific form, and no alternative formulation has demonstrated superior effectiveness in well-controlled trials [21].

Among alternatives, creatine citrate offers greater water solubility and may cause less gastrointestinal discomfort in sensitive individuals, though its bioavailability is considered comparable to monohydrate [2]. Creatine ethyl ester was developed to improve membrane permeability and reduce reliance on the creatine transporter, but is not recommended for pregnant or breastfeeding women, children, or individuals with hepatic or renal dysfunction due to its ethanol content [2]. Creatine gluconate combines creatine with glucose to potentially

enhance muscle uptake via insulin-mediated transport, though evidence supporting superiority over monohydrate remains insufficient [2]. Creatine magnesium chelate, in which creatine is bound to magnesium — a cofactor in the creatine kinase reaction — may offer synergistic metabolic benefits, but likewise lacks robust comparative evidence [2]. Creatine monohydrate should be considered the preferred form for both athletic and clinical applications given its unmatched evidence base and cost-effectiveness [2,21]. Alternative forms may be considered on an individual basis — for example in cases of gastrointestinal intolerance to monohydrate — but should not be regarded as superior substitutes in the absence of compelling comparative data [21].

6. Clinical Applications.

6.1. Neurodegenerative Diseases and Traumatic Brain Injury

The central nervous system is among the most metabolically demanding tissues in the human body, relying on a continuous and stable supply of ATP to maintain neuronal function. Given creatine's fundamental role in cellular energy homeostasis, its therapeutic potential in neurodegenerative diseases has attracted considerable scientific interest [22]. Conditions such as Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and Huntington's disease (HD) are characterised by progressive neuronal loss preceded by disruptions in brain energetics — metabolic impairments that often emerge prior to the clinical manifestation of symptoms, suggesting a critical window for early intervention [22]. Beyond energy provision, creatine may exert beneficial effects across several pathways commonly implicated in neurodegeneration, including mitochondrial dysfunction, oxidative stress, calcium dysregulation, and neuroinflammation [22].

Despite a compelling mechanistic rationale, clinical evidence for the efficacy of creatine in neurodegenerative diseases remains uneven. In Alzheimer's disease, the single-arm pilot CABA study conducted in 20 patients demonstrated that 8 weeks of creatine supplementation at 20 g/day was well tolerated, was associated with an 11% increase in brain creatine concentration as measured by magnetic resonance spectroscopy, and with improvements across a range of cognitive tests from the NIH Toolbox battery [23]. The authors emphasise, however, that as a single-arm trial without a control group it cannot establish efficacy, and that observed improvements may reflect practice effects or placebo response — larger randomised controlled trials are needed [23]. In Parkinson's disease, available clinical evidence has not confirmed the

efficacy of creatine to date. A Cochrane review encompassing two RCTs with a total of 194 patients found no significant benefits in motor function, activities of daily living, or quality of life, based on low-quality evidence [24]. More critically, the LS-1 trial — one of the largest RCTs in the history of Parkinson's disease research, enrolling 1,741 patients receiving creatine at 10 g/day for a minimum of 5 years — was terminated early for futility, demonstrating no effect on disease progression across any of five clinical outcome domains [25]. In Huntington's disease, the CREST-E trial — the largest, longest, and highest-dose study of creatine in any neurological condition to date, enrolling 553 patients receiving up to 40 g/day for up to 48 months — was likewise terminated early for futility, with no benefit observed in the rate of functional decline [26]. A key methodological limitation across existing studies is the widespread absence of direct brain creatine quantification, making it impossible to determine whether supplementation protocols were sufficient to meaningfully increase brain creatine availability [22]. It is also worth noting that the clinical symptoms of neurodegenerative diseases typically emerge only after substantial and often irreversible neuronal loss has already occurred, which may explain why even cellular-level neuroprotection does not necessarily translate into measurable clinical benefits when supplementation begins at an advanced disease stage [22].

The case for creatine in traumatic brain injury (TBI) rests on a compelling mechanistic rationale. Following TBI, oxidative phosphorylation is impaired due to reduced cerebral blood flow and oxygen availability, while ATP demand increases dramatically — conditions under which the PCr-Cr system, operating independently of oxygen, represents a critical energy buffer [27]. Brain creatine levels have been shown to decline following TBI, with longitudinal studies reporting reduced concentrations in contact sport athletes exposed to repetitive sub-concussive impacts across a competitive season [27]. In the randomised clinical trial by Sakellaris et al., children and adolescents with moderate to severe TBI receiving creatine supplementation at 0.4 g/kg/day for 6 months showed improved cognitive and behavioural outcomes, reduced headaches, dizziness, and fatigue, and a shortened duration of post-traumatic amnesia and intensive care unit stay [27]. Experimental evidence further suggests that prophylactic creatine supplementation prior to TBI may reduce cortical tissue damage in animal models, and that pre-injury supplementation attenuated cognitive decrements during hypoxia in humans — indicating potential prophylactic value for high-risk populations such as athletes and military personnel [27,28]. Beyond classical TBI, creatine has also been investigated in spinal cord injury — animal studies demonstrated reductions in tissue scarring and improvements in motor function, while human studies reported improvements in aerobic capacity and muscle strength

[27]. It must be noted, however, that clinical evidence in TBI and spinal cord injury in humans remains largely confined to small studies and to date best documented in paediatric populations, and the efficacy of creatine in adult populations requires confirmation in well-designed clinical trials [27,28].

6.2. Ageing, Sarcopenia, and Cognitive Function.

Sarcopenia — the progressive, age-related loss of muscle mass, strength, and physical performance — represents one of the most clinically significant consequences of ageing, adversely affecting mobility, autonomy, and quality of life [29,30]. The pathophysiology of sarcopenia involves multiple interconnected mechanisms, including mitochondrial dysfunction, chronic low-grade inflammation known as inflamm-aging, impaired satellite cell activity, and a decline in anabolic hormonal signalling — all contributing to accelerated muscle protein catabolism and impaired regenerative capacity [8,29,30]. Notably, geriatric populations exhibit 30–40% lower baseline phosphocreatine stores compared to young adults, which directly impairs the capacity to sustain high-intensity effort and may underlie accelerated functional deterioration [31].

Creatine supplementation, particularly when combined with resistance training, has emerged as one of the most evidence-supported strategies to counteract sarcopenia. By elevating intramuscular phosphocreatine stores and enhancing the capacity for rapid ATP regeneration, creatine consistently augments muscle mass and strength in older adults [8,29,30]. Meta-analyses confirm that creatine combined with resistance training yields greater gains in lean body mass, lower limb strength, and functional capacity compared to resistance training alone [8,29,31]. A recent meta-analysis encompassing 8 RCTs with a total of 482 participants demonstrated that creatine combined with resistance training significantly improved lower limb strength (SMD = 0.29) and lean tissue mass (SMD = 0.27), with subgroup analysis revealing an important temporal effect — interventions lasting up to 32 weeks produced markedly superior outcomes compared to longer protocols, potentially reflecting adaptive saturation with prolonged supplementation [31]. Clinically meaningful improvements have been demonstrated in chair-rise performance — a validated predictor of fall risk — with creatine-supplemented participants showing a 23% improvement versus 16% in placebo groups, and a 5–8% increase in lower limb strength potentially translating to an approximately 20% reduction in fall risk [29,31]. Walking speed and overall functional independence have also been reported to improve, suggesting that the benefits of creatine extend to activities of daily living [8,29]. Both

loading protocols (20 g/day for 5–7 days followed by 3–5 g/day maintenance) and continuous low-dose protocols (3–5 g/day without loading) have demonstrated efficacy in older populations, with the latter generally better tolerated [29,30].

Beyond sarcopenia, emerging evidence highlights the importance of the age-related decline in muscular power — termed powerpenia — which occurs earlier and has a greater impact on mobility and fall risk than strength loss alone [8]. Creatine supplementation combined with high-velocity resistance training has been shown to enhance lower-limb power and rate of force development in older adults, with implications for the preservation of functional independence [8]. The anti-inflammatory properties of creatine may further contribute to its benefits in ageing populations — creatine has been shown to suppress neutrophil adhesion, attenuate pro-inflammatory cytokines including TNF-α, IL-1β, and CRP following intense exercise, and reduce markers of oxidative stress, collectively targeting key drivers of inflamm-aging [29]. Evidence further suggests that creatine may activate the mTORC1 pathway through osmotic stress induced by increased cellular hydration, potentially stimulating ribosomal biogenesis and myofibrillar protein accretion — representing an additional mechanism underlying the synergy between creatine and resistance training in the context of sarcopenia [31].

Regarding bone health, the evidence is more equivocal. Although creatine may stimulate osteoblast activation and reduce markers of bone resorption in some studies, a meta-analysis encompassing 5 RCTs with 193 participants found no significant effect of creatine combined with resistance training on bone mineral density at the hip, femoral neck, lumbar spine, or whole body [32]. An interesting exception concerns studies employing relative creatine dosing (0.1 g/kg/day) combined with higher training frequency (3 days/week) — only these protocols demonstrated beneficial effects on bone mineralisation, suggesting that dose and training frequency may be critical determinants of efficacy in this domain [32]. The most promising findings come from longer interventions — a 12-month study in postmenopausal women demonstrated that creatine supplementation attenuated femoral neck bone mineral density loss compared to placebo (1.2% vs 3.9%) [29]. The indirect effect of creatine on bone — mediated through increased muscle mass and consequently greater mechanical loading during contraction — may require longer timeframes to manifest as measurable changes in bone mineral density [29,30,32].

Beyond its musculoskeletal effects, creatine has attracted growing interest as a potential modulator of cognitive function in ageing. The mechanistic rationale is compelling — brain creatine availability declines with age, and the ATP-PCr system plays a fundamental role in sustaining neuronal energy metabolism during cognitively demanding tasks [8,33]. The brain-

specific isoform of creatine kinase (BB-CK) supports persistent ATP regeneration in neural tissue, thereby facilitating cognitive task performance, neurotransmitter synthesis, synaptic plasticity, and reduction of oxidative stress in synaptic vesicles [33]. Ageing is also associated with reduced physical activity and lower dietary creatine intake, both of which may further deplete brain creatine reserves and increase vulnerability to cognitive decline [8,33].

A systematic review examining creatine and cognition specifically in older adults found that five of six included studies reported a positive association between creatine and cognitive performance, particularly in the domains of memory and attention, though the overall quality of evidence remains limited — half of the included studies received a methodological quality rating of "poor" [33]. In interventional studies, creatine supplementation at 20 g/day for 7 days improved forward number recall, spatial recall, and long-term memory in adults with a mean age of 76 years [33]. Meta-analytic evidence further supports improvements in memory performance specifically in older adults aged 66–76 years, with an effect size of SMD = 0.88 — considerably larger than that observed in younger populations — suggesting an age-specific benefit driven by lower baseline creatine levels and greater metabolic demands of cognitive tasks in older individuals [8]. Additional benefits have been reported for processing speed (SMD = −0.51) and attention (SMD = −0.31), though the overall certainty of evidence remains moderate to low due to small sample sizes, heterogeneous methodologies, and short intervention durations [8,33].

The combination of creatine supplementation with structured exercise appears to produce synergistic rather than merely additive effects on both physical and cognitive outcomes [8]. Exercise promotes neuroplasticity through myokine signalling — including BDNF, irisin, and IGF-1 — while creatine augments the energetic substrate available for both muscular contraction and neural function [8]. Together, these interventions reinforce the muscle-brain axis, with combined protocols consistently demonstrating greater improvements in strength, lean mass, functional capacity, and cognitive performance than either intervention alone [8]. From a practical standpoint, combining 3–5 g/day of creatine monohydrate with a structured resistance training programme of at least 2–3 sessions per week represents a safe, cost-effective, and evidence-based strategy for healthy ageing — addressing sarcopenia, fall risk, and cognitive decline within a single intervention framework [8,29,30].

6.3. Skeletal Muscle Diseases.

Hereditary and acquired muscle diseases are characterised by progressive muscle weakness for which curative therapies remain largely unavailable, making symptomatic and supportive interventions of particular clinical importance [34]. Given creatine's fundamental role in muscle energy metabolism and its well-documented ergogenic effects in healthy populations, its therapeutic potential in primary muscle diseases has attracted considerable scientific interest. The rationale for supplementation in these conditions is straightforward — reduced intramuscular PCr availability and impaired CK/PCr system function are common features of many myopathies, and exogenous creatine supplementation may partially restore the energetic deficit underlying muscle weakness [2,35].

The strongest evidence for creatine's therapeutic utility in muscle diseases derives from a Cochrane systematic review by Kley et al. encompassing 14 randomised controlled trials with 364 participants [34]. A meta-analysis of six trials in muscular dystrophies demonstrated a statistically significant increase in muscle strength in the creatine group compared to placebo, with a mean difference of 8.47% (95% CI: 3.55–13.38) [34]. Notably, pooled data from four trials showed that a significantly greater proportion of participants reported feeling better during creatine treatment compared to placebo, with a risk ratio of 4.51 (95% CI: 2.33–8.74) [34]. Improvements in functional performance were also observed in idiopathic inflammatory myopathies, and creatine was well tolerated across all studied populations with no clinically relevant adverse events reported [34]. These findings provide evidence that short- and medium-term creatine supplementation increases muscle strength in muscular dystrophies and improves functional performance in both muscular dystrophies and inflammatory myopathies [34,35].

In the specific context of inflammatory myopathies, a randomised controlled trial by Alexanderson et al. enrolling 37 patients with polymyositis or dermatomyositis — all receiving stable immunosuppressive therapy and/or corticosteroids — demonstrated that 6-month creatine supplementation (20 g/day for 8 days, then 3 g/day) combined with a home exercise programme significantly improved aggregate functional performance time compared to placebo (median improvement 13% vs 3%, $p = 0.029$) [36]. The phosphocreatine-to-beta-nucleoside triphosphate ratio measured by MRS increased significantly in the creatine group, confirming that the observed functional benefits reflect genuine improvements in muscle bioenergetics [36]. No clinically relevant adverse events were observed, and the authors note that creatine represents a safe, effective, and inexpensive adjunct to treatment in these conditions [36].

The picture is more complex across individual dystrophy subtypes. In myotonic dystrophy type 1 (DM1), a randomised crossover trial in 34 patients found no significant improvements in muscle strength, activities of daily living, or patients' global self-assessment following 8 weeks of creatine supplementation, though creatine was well tolerated without clinically relevant side effects [37]. These results are consistent with the Cochrane review findings showing no benefit of creatine in metabolic myopathies and myotonic dystrophy [34]. In Duchenne muscular dystrophy (DMD), available clinical data are equivocal — some studies have reported improvements in grip strength or cellular energy parameters, while others have found no significant benefits in muscle strength or motor function across various doses and supplementation durations [38]. A review of the literature in paediatric populations confirms this heterogeneity — while creatine supplementation in young athletes consistently improves physical performance, effects in children and adolescents with muscle diseases such as DMD, spinal muscular atrophy, or juvenile dermatomyositis are largely absent or inconsistent, which may reflect the heterogeneity of protocols and small sample sizes across available trials [38].

At the molecular and tissue level, studies in a murine model of Duchenne muscular dystrophy provide additional insight into the mechanisms of creatine action in diseased muscle [39]. DMD is characterised by a deficiency of dystrophin — a protein critical for sarcolemmal stability and myofibrillar integrity — leading to progressive muscle damage and fibrosis [39]. A study by Fernandes et al. demonstrated that 8 weeks of creatine supplementation in MDX mice was associated with reduced inflammatory infiltrates, better preservation of intramuscular glycogen, decreased tissue fibrosis, and a reduction in cellular pseudohypertrophy [39]. These observations suggest that creatine may not only improve energy availability in diseased muscle but also modulate inflammatory processes and slow the progression of tissue degeneration — though these findings require confirmation in well-designed clinical trials in humans [35,39].

A distinct category is represented by primary creatine synthesis deficiencies — rare congenital enzymatic or transporter defects (AGAT, GAMT, or CRTR deficiencies) leading to markedly reduced brain and muscle creatine and PCr concentrations [3,35]. Clinical manifestations include psychomotor delay, intellectual disability, speech disorders, epilepsy, and myopathies [3,35]. In contrast to acquired dystrophies, in these congenital conditions long-term high-dose creatine supplementation (0.3–0.8 g/kg/day) represents the primary therapeutic strategy, demonstrating the ability to increase brain creatine concentrations and improve or stabilise clinical symptoms — with greatest efficacy when treatment is initiated in early childhood [3,35].

6.4. Depressive and Psychiatric Disorders.

Major depressive disorder is among the most prevalent and burdensome psychiatric conditions worldwide, and a substantial proportion of patients fail to achieve adequate remission with first-line pharmacological treatments. Impaired brain energy metabolism has emerged as a key pathophysiological feature of depression — lower creatine and phosphocreatine concentrations in the prefrontal cortex have been directly associated with greater depression severity, while higher baseline brain PCr levels predict favourable treatment response [40]. This bioenergetic framework provides a compelling mechanistic rationale for creatine supplementation as a potential adjunct to conventional antidepressant strategies [40].

The mechanisms through which creatine may exert antidepressant effects are multifactorial. By restoring PCr availability in the prefrontal cortex and hippocampus, creatine supports neuronal energy homeostasis — a precondition for effective neurotransmitter synthesis and synaptic plasticity [40]. Preclinical evidence demonstrates that creatine modulates serotonergic and dopaminergic systems, both of which are central targets of conventional antidepressant pharmacotherapy [40]. Animal studies have shown that creatine reduces depressive-like behaviour, restores BDNF levels in the hippocampus, increases synaptic proteins such as PSD95, and exerts rapid antidepressant effects through the PI3K/Akt/mTOR pathway — a mechanism shared with ketamine [40]. Rodent studies have further revealed a marked sexual dimorphism in creatine's antidepressant-like effects — effects were consistently observed in females, while results in males were equivocal or opposite, suggesting that sex hormones, particularly oestradiol and progesterone, modulate brain creatine kinase activity and may amplify creatine's effects under conditions of metabolic dysregulation [41]. This sex-dependence carries important implications for the interpretation of clinical trial results, in which the vast majority of participants have been women [41].

Clinical evidence for creatine's antidepressant potential has accumulated steadily, though its interpretation warrants caution. The first systematic meta-analysis of this topic — encompassing 11 trials with 1,093 participants, published by Eckert et al. in the British Journal of Nutrition in 2025 — found a statistically significant but small reduction in depressive symptoms (SMD = −0.34; 95% CI: −0.68 to 0.00), equivalent to 2.2 points on the Hamilton Depression Rating Scale, below the minimal important difference of 3.0 points [42]. The GRADE assessment rated the evidence as very low quality, with substantial heterogeneity (I^2 = 71.3%) [42]. Results for secondary endpoints were significant for remission (odds ratio 3.60;

95% CI: 1.76–7.56 across three trials), though sensitivity analyses indicated substantial bias favouring creatine [42]. The authors conclude that creatine may offer small-to-moderate benefits in depression, but that the true effect may be trivial or null, requiring confirmation in larger and more rigorous trials [42].

Among individual clinical trials, a randomised, double-blind, placebo-controlled trial by Lyoo et al. demonstrated that augmentation of escitalopram with creatine at 5 g/day for 8 weeks in women with major depressive disorder yielded a large effect size (Cohen's d = 1.13; 95% CI: 0.75–1.52) on the Hamilton Depression Rating Scale — among the largest reported for any augmentation strategy in depression [43]. In a neuroimaging subsample of 34 patients, creatine augmentation increased prefrontal N-acetylaspartate levels and enhanced rich club hub connections in brain structural networks, confirming that the observed clinical benefits are underpinned by genuine changes in brain energy metabolism and neural network organisation [44]. A pilot randomised controlled trial by Sherpa et al. demonstrated that combining creatine monohydrate (5 g/day) with cognitive-behavioural therapy for 8 weeks significantly reduced PHQ-9 depression scores compared to placebo plus CBT (mean difference = −5.12 points), with comparable acceptability and tolerability between groups [45]. Notably, the augmenting effect of creatine on CBT was observed regardless of sex, increasing the generalisability of these findings beyond the predominantly female samples of earlier trials [45].

A dose-ranging study using ^{31}P magnetic resonance spectroscopy in adolescent girls with SSRI-resistant depression demonstrated that creatine supplementation at doses of 2, 4, and 10 g/day for 8 weeks was associated with tendencies toward increases in frontal lobe PCr of 4.6%, 4.1%, and 9.1% respectively, while frontal lobe PCr tended to decrease by 0.7% in the placebo group [46]. A significant inverse correlation was found between frontal lobe PCr and depression scale scores across the entire sample ($p = 0.02$), providing direct evidence of target engagement with brain bioenergetics [46]. An open-label pilot study by Kious et al. investigated the combination of creatine (5 g/day) with 5-hydroxytryptophan (100 mg twice daily) as augmentation of SSRI/SNRI in 15 women with treatment-resistant depression, yielding a 60% reduction in HAM-D scores ($p < 0.00001$) with no serious adverse events — though as an open-label trial without a control group, these results require cautious interpretation [47].

The negative result of a pilot dose-finding study by Nemets et al. in patients not responding to SSRI/SNRI after 3 weeks of treatment — where creatine at 5 or 10 g/day demonstrated no significant advantage over placebo during a 4-week augmentation period (N=18) — underscores that response to creatine may depend on baseline brain PCr stores, treatment duration, and the specific clinical context [48]. The observation that two female patients in the

creatine group showed early improvement exceeding a 50% reduction in Hamilton scores while none in the placebo group did, suggests possible individual-level heterogeneity of response [48].

Particular caution is warranted regarding the use of creatine in patients with bipolar affective disorder. A randomised controlled trial by Toniolo et al. enrolling 35 patients with bipolar depression demonstrated that despite the absence of a statistically significant difference in the primary outcome (change in MADRS, $p = 0.560$), remission rates were significantly higher in the creatine group than in the placebo group both among all randomised patients (52.9% vs 11.1%; $p = 0.012$; OR = 9.0) and among completers (66.7% vs 18.2%; $p = 0.036$) [49]. However, two patients in the creatine group switched to hypomania and mania respectively within the first two weeks of treatment [49]. A consistent safety signal comes from the independent, though small, study by Roitman et al., in which both bipolar patients enrolled experienced a similar switch, while no such event occurred among the unipolar participants [50]. The proposed mechanism is biologically plausible — creatine, by enhancing mitochondrial energy production, may potentially trigger manic episodes in susceptible individuals, given that mania is associated with a state of elevated neuronal energy availability [49,50]. Patients with a confirmed history of mania or bipolar affective disorder should therefore be considered at elevated risk, and creatine supplementation in this population should only be undertaken under close psychiatric supervision [49,50].

Collectively, current evidence positions creatine as a promising, accessible, and well-tolerated adjunctive strategy for depression — particularly when combined with established psychological or pharmacological treatments — though larger, longer, and more rigorously designed clinical trials are urgently needed to confirm its efficacy, define optimal protocols, and establish which populations derive the greatest benefit [40,42,43,45].

6.5. Type 2 Diabetes and Metabolic Syndrome.

Type 2 diabetes mellitus is a chronic metabolic disorder characterised by sustained hyperglycaemia resulting from impaired insulin secretion by pancreatic β cells, insulin resistance, or both [51]. Chronic hyperglycaemia in diabetes is associated with a range of cardiometabolic disturbances, including hypertension, dyslipidaemia, atherosclerosis, and visceral obesity — the constitutive components of metabolic syndrome, which represents a major risk factor for cardiovascular disease [51,52]. Global epidemiological data indicate that the number of people living with diabetes nearly doubled between 1990 and 2022, with

projections estimating an increase to 853 million by 2050 [53]. Skeletal muscle plays a central role in this pathophysiology — under euglycaemic conditions it accounts for more than 70–80% of insulin-mediated glucose disposal, and when muscle mass declines and insulin signalling is impaired, the capacity for glucose uptake deteriorates, further worsening glycaemic control [51,53,54]. Creatine has attracted growing interest as a potential adjunctive strategy in this context, owing to its multifaceted effects on glucose metabolism, lipid profile, and cardiovascular function [51,52,54,55].

The most compelling mechanistic evidence for creatine's role in glucose metabolism centres on its ability to regulate the expression and membrane translocation of GLUT-4 — the primary insulin-regulated glucose transporter in skeletal muscle [51,54]. Animal studies demonstrated that creatine supplementation increased GLUT-4 protein content by 60–100% across multiple skeletal muscle groups, while concomitantly enhancing insulin-stimulated glucose transport rates approximately twofold compared to controls [57]. The proposed molecular mechanism is multistep: creatine induces phosphorylation of AMP-activated protein kinase (AMPK) — a master regulator of cellular energy homeostasis — which in turn increases the activity of the transcription factor MEF2, directly regulating GLUT-4 gene expression [51,54,57]. Notably, these effects may occur independently of changes in intramuscular creatine or phosphocreatine concentrations, suggesting that creatine influences muscle glucose metabolism through mechanisms beyond simple energy buffering [57]. Creatine may also stimulate insulin secretion by pancreatic β cells in vitro, enhance muscle glycogen storage through osmosensing and PKBα/Akt1 activation, and augment post-exercise glycogen resynthesis when combined with carbohydrate ingestion — although insulinotropic effects have not been confirmed in clinical studies [51,54]. In humans, creatine supplementation has been shown to prevent the decline in muscle GLUT-4 content during two weeks of immobilisation and to increase GLUT-4 protein levels by approximately 40% during subsequent rehabilitation training [58].

Clinical evidence regarding creatine's effects on glycaemic control in type 2 diabetes remains promising but limited. A randomised, double-blind, placebo-controlled trial enrolling 25 adults with type 2 diabetes demonstrated that creatine supplementation at 5 g/day for 12 weeks, combined with a programme of aerobic and resistance exercise performed three times per week, significantly reduced HbA1c and postprandial glycaemia compared to placebo, with no effect on insulin or C-peptide concentrations [51,53]. The improvement in glycaemic control was associated with enhanced GLUT-4 translocation to the sarcolemma rather than an increase in total muscle GLUT-4 protein content, and the reduction in HbA1c correlated with increased AMPK-α expression [51,54]. A separate trial in healthy sedentary men demonstrated that

creatine combined with moderate-intensity aerobic training significantly reduced the glucose area under the curve during an oral glucose tolerance test compared to exercise alone ($p = 0.034$), without affecting insulin resistance as measured by HOMA [59]. A systematic review and meta-analysis encompassing nine trials found no statistically significant effects of creatine on fasting blood glucose (SMD: 0.05; 95% CI: −0.53 to 0.63) or insulin resistance (SMD: −0.38; 95% CI: −0.90 to 0.14) [60]. The authors note, however, that only two of the nine trials were conducted specifically in diabetic individuals — and both reported positive effects — highlighting the need for dedicated trials in this population [60]. A broader meta-analysis assessing creatine's effects on metabolic parameters confirmed statistically significant benefits over placebo, particularly in individuals over 50 years of age combining creatine with resistance training, although the heterogeneity of populations and protocols limits extrapolation to patients with type 2 diabetes [61]. The discrepancy between mechanistic and clinical data most likely reflects the limited number of trials conducted specifically in diabetic individuals, the heterogeneity of supplementation protocols, and the consistent observation that benefits are most pronounced when creatine is combined with structured physical exercise [51,53,54,60].

Beyond its direct effects on glucose metabolism, creatine may favourably modify other components of metabolic syndrome. Clinical studies have demonstrated that creatine supplementation reduces LDL-cholesterol and total cholesterol concentrations, increases functional capillary density and microvascular reactivity, and may lower homocysteine levels in individuals with hyperhomocysteinaemia — an independent cardiovascular risk factor [52,55]. In an animal model of diabetes, creatine significantly reduced triglycerides, total cholesterol, and LDL-C while increasing HDL-C, and decreased coronary vascular permeability — suggesting a protective effect on vascular endothelium under hyperglycaemic conditions [55]. The proposed vasoprotective mechanism involves creatine's antioxidant properties — its ability to directly scavenge free radicals and limit mitochondrial reactive oxygen species production — which may increase nitric oxide bioavailability and improve endothelial function, both of which are impaired in metabolic syndrome and type 2 diabetes [55]. The anti-inflammatory properties of creatine, including attenuation of TNF-α and IL-6, may additionally contribute to improvements in insulin sensitivity, given that chronic low-grade inflammation is a well-established driver of insulin resistance [52,53,54].

A clinically important intersection exists between type 2 diabetes and sarcopenia — a condition that co-occurs in up to 30% of hospitalised patients with diabetes and creates a vicious cycle of mutually reinforcing metabolic and musculoskeletal deterioration [53,63]. Loss of muscle mass worsens insulin sensitivity and glycaemic control, while hyperglycaemia in turn accelerates

muscle catabolism through inflammatory and oxidative mechanisms, creating a pathophysiological feedback loop [8,53]. A systematic review of 20 randomised trials enrolling 1,093 participants confirmed that combining creatine with exercise training significantly increases muscle strength and reduces body fat percentage in older adults [64]. By counteracting sarcopenia — which independently worsens insulin resistance and glycaemic control — creatine may exert indirect glycaemic benefits beyond its direct effects on GLUT-4 expression and glucose transport [53,54,63].

Despite this encouraging evidence, a meaningful translational gap persists between mechanistic promise and clinical outcomes [53,54]. Existing clinical trials in diabetic populations are small, short-term, and heterogeneous with respect to supplementation protocols and concomitant pharmacological treatment, precluding firm clinical recommendations [51,53,54,60]. Future trials specifically designed for type 2 diabetes populations, with adequate sample sizes, longer follow-up periods, direct assessment of molecular markers, and integration with standard-of-care pharmacological therapies, are urgently needed to translate the compelling mechanistic evidence into actionable clinical guidance [51,53,54,60].

6.6. Cancer-Related Cachexia and Oncology.

Cancer cachexia is a multifactorial metabolic syndrome characterised by progressive skeletal muscle wasting, loss of body weight, and systemic inflammation — occurring in up to 80% of cancer patients and directly contributing to reduced tolerance to treatment, impaired quality of life, and increased mortality [65,66]. Low muscle mass in individuals with cancer has a profound impact on independence and quality of life and is associated with greater treatment toxicity and poorer prognosis [67]. Unlike simple starvation, cachexia involves a complex interplay of pro-inflammatory cytokines, proteolysis-inducing factors, and disrupted energy metabolism that renders conventional nutritional interventions largely insufficient [66]. Given creatine's fundamental role in cellular energy homeostasis, muscle mass preservation, and anti-inflammatory signalling, it has attracted growing interest as a potential adjunctive strategy in the oncological setting [65,66,67].

The mechanistic rationale for creatine supplementation in cancer cachexia is compelling. In cachectic conditions, intramuscular PCr availability is reduced, ATP resynthesis is impaired, and the CK/PCr energy buffering system is disrupted — directly contributing to muscle weakness and accelerated protein catabolism [65]. Preclinical evidence demonstrates that creatine supplementation modulates cellular energy metabolism and attenuates cancer

cachexia-associated muscle wasting through multiple pathways, including restoration of PCr stores, reduction of oxidative stress, suppression of pro-inflammatory cytokine signalling, and preservation of mitochondrial function [65]. The antioxidant and anti-inflammatory properties of creatine — including its capacity to reduce reactive oxygen species, protect cell membranes from lipid peroxidation, and attenuate TNF-α and IL-6 — may further help counteract the oxidative stress that is both a driver and a consequence of cancer-associated muscle wasting [65,68]. An important mechanism underlying creatine's potential efficacy in the oncological setting is its ability to enhance the quality and volume of resistance exercise training — by increasing intramuscular PCr stores, creatine may enable patients to recover more effectively between exercise sets, accumulating over time into greater muscle adaptations than exercise alone can achieve [67].

Beyond its direct effects on muscle preservation, creatine has emerged as a potential modulator of antitumour immunity. Preclinical studies identified creatine as an important metabolic regulator that conserves bioenergy to power CD8+ T cell antitumour reactivity within the metabolically challenging tumour microenvironment, with creatine supplementation demonstrating synergistic efficacy with PD-1/PD-L1 immune checkpoint blockade therapy [69]. The proposed mechanism involves ATP/AMPK-mediated regulation of T cell receptor signalling pathways [69]. This picture is considerably complicated, however, by the observation that creatine has two faces in oncology — while it suppresses subcutaneous tumour growth and enhances antitumour immunity, orthotopic mouse models have demonstrated that creatine may promote invasion and metastasis of colorectal, pancreatic, and breast cancer through activation of the Smad2/3 pathway [70]. This fundamental ambiguity warrants particular caution in extrapolating preclinical data to clinical recommendations [70].

Clinical evidence in cancer patients remains very limited. A PRISMA-compliant systematic review encompassing seven trials with a total of 463 participants found that creatine supplementation does not demonstrate a significant effect on body composition compared to placebo in oncological populations [71]. None of the three trials assessing lean body mass found a significant between-group difference, though all reported increases in both groups — likely attributable to concurrent resistance training [71]. Fat mass results were variable, showing reductions, no changes, or attenuation of gains during hormone therapy [71]. The review authors conclude that creatine supplementation appears safe and may be more beneficial with less aggressive treatment regimens or in non-metastatic cases, but that the absence of significant between-group differences may reflect methodological limitations — including intervention durations below 8–10 weeks, small sample sizes, and high dropout rates [71]. An independent

review of nutraceuticals in cancer cachexia, which identified only two clinical trials evaluating creatine, reached a similar conclusion — well-designed trials do not support a benefit on body weight, muscle mass, or quality of life in this population, though the authors note that creatine may be more efficacious when combined with resistance exercise [72].

Among individual clinical trials, results are consistently negative or mixed. A large multicentre RCT enrolling 263 patients with incurable cancer and the cancer anorexia/weight loss syndrome found no effect of creatine on body weight, appetite, grip strength, body composition, or survival [73]. A trial in 31 colorectal cancer patients undergoing chemotherapy found no effect on muscle mass or function, with improvement in phase angle observed only in a subgroup receiving less aggressive chemotherapy [74]. Two trials in prostate cancer patients undergoing androgen deprivation therapy found that adding creatine to a resistance training programme conferred no additional benefit over training alone with respect to lean mass, muscle strength, or physical function [75]. Similarly, a trial in head and neck cancer patients undergoing resistance training found no additional benefit of creatine supplementation on lean body mass [76], and a study in paediatric oncology patients reported no significant improvements in muscle function [77]. It is important to note, however, that the heterogeneity of cancer types, treatment protocols, and supplementation regimens across studies substantially complicates the interpretation of pooled results and may obscure benefits in specific patient subgroups [67,71].

A registered randomised controlled trial is currently investigating the effects of 52 weeks of creatine supplementation combined with resistance training in 200 patients with metastatic castration-sensitive prostate cancer receiving androgen deprivation therapy [78]. This trial may provide the first robust long-term clinical data on creatine supplementation in this population and address whether intervention duration is a critical determinant of efficacy [78].

Collectively, current clinical evidence is insufficient to support definitive recommendations for the routine use of creatine in cancer cachexia or as a muscle preservation strategy in oncology [71,72]. At the same time, promising preclinical data on antitumour immunometabolism, selective positive signals in patients receiving less aggressive treatments, and the potential for synergy with resistance exercise training justify continued translational research — provided it is conducted with full recognition of the dual nature of creatine's effects in cancer biology, and with adequate sample sizes, longer intervention durations, and clinically meaningful endpoints such as physical function and quality of life [35,67,69,70,71,72].

7. Safety of Creatine Supplementation.

7.1. General Safety Profile.

Creatine monohydrate is one of the most extensively studied dietary supplements in the history of sports medicine. A comprehensive analysis of 685 randomised controlled trials encompassing more than 12,800 participants — across populations ranging from infants to the elderly, at doses up to 30 g/day for periods of up to 14 years — found that the frequency of reported adverse effects was comparable between creatine and placebo groups: 13.7% of studies in the creatine group reported any side effect versus 13.2% in the placebo group, with no statistically significant difference ($p = 0.776$) [79]. Analysis of 28.4 million adverse event reports from databases in the USA, Canada, Australia, and Europe revealed that creatine was mentioned in only 0.00072% of cases, with a substantial proportion of these reports involving products not containing creatine or its use in combination with other substances [79]. Creatine monohydrate has been granted GRAS (Generally Recognized as Safe) status by the United States Food and Drug Administration and is the only form of creatine to have undergone full regulatory safety evaluation by the FDA and its equivalents in key global markets — other commercially available forms of creatine do not hold equivalent formal regulatory approval [52,79,80]. A comprehensive position statement published in 2025 concluded that creatine monohydrate is safe and beneficial throughout the lifespan, from childhood to old age [81].

The most commonly reported side effect is transient body mass gain during the loading phase, attributable to increased intracellular water retention rather than fat accumulation [80]. Gastrointestinal distress — including bloating, nausea, and cramping — is infrequent and most commonly associated with high single doses exceeding 10 g [5,80]. Dividing the daily dose into smaller amounts of 5 g or less substantially reduces the likelihood of gastrointestinal discomfort [5,80]. Claims that creatine causes dehydration, thermoregulatory disturbances, or muscle cramps are unsupported by controlled clinical research — available evidence suggests that creatine may in fact support thermoregulation and reduce the incidence of muscle cramps during exercise [80].

7.2. Renal Safety.

The most persistent concern regarding creatine relates to its potential nephrotoxicity, arising from the observation that supplementation consistently elevates serum creatinine — a widely

used marker of glomerular filtration rate — which may be misinterpreted as evidence of renal impairment [5]. The mechanism is purely pharmacokinetic: creatine undergoes non-enzymatic, irreversible conversion to creatinine at a rate of approximately 2 g/day, and supplementation, by increasing the body's total creatine pool, proportionally increases creatinine production and serum concentrations [5,82]. This represents a metabolic confound rather than a pathological process.

The distinction between elevated serum creatinine and actual renal dysfunction is critical and well-supported by the literature. A meta-analysis of 21 studies confirmed that creatine supplementation is associated with a small but statistically significant increase in serum creatinine (MD: 0.07 μmol/L; 95% CI: 0.01–0.12), but found no significant differences in glomerular filtration rate between creatine and control groups — indicating preserved kidney function [83]. The creatinine elevation was most pronounced during the loading phase (≤1 week), with no significant effect observed between 1 and 12 weeks [83]. An independent narrative review covering studies published between 2020 and 2024 confirmed that creatine supplementation is safe for renal function in both healthy individuals and patients with pre-existing renal conditions [84]. Long-term studies extending up to 21 months in athletes and up to 5–8 years in patients with Parkinson's disease consistently showed no clinically significant deterioration in renal parameters [5]. Case reports linking creatine to renal failure are characterised by serious methodological limitations — including retrospective designs, concurrent use of anabolic steroids or other nephrotoxic substances, and pre-existing renal disease — which substantially limits their attributability to creatine alone [5].

7.3. Hepatic Safety.

Concerns regarding hepatotoxicity have appeared in isolated case reports and some animal studies involving excessive doses [85]. However, a large cross-sectional population study using data from the 2017–2018 NHANES survey encompassing 5,957 participants found no association between dietary creatine intake and liver fibrosis, cirrhosis, or hepatic steatosis [85]. Binary logistic regression adjusted for age, sex, BMI, total energy intake, and alcohol consumption demonstrated that consuming ≥2 g/day of dietary creatine did not significantly increase the risk of any liver condition [85]. Case reports suggesting hepatotoxicity typically involved concurrent use of multiple supplements, anabolic substances, or alcohol, which substantially limits their attributability to creatine alone [85].

7.4. Creatine in Chronic Kidney Disease — A Paradox.

Contrary to the widespread assumption that creatine is harmful to diseased kidneys, emerging evidence suggests that patients with CKD may in fact suffer from creatine deficiency [6,86]. The kidneys play a critical role in the first enzymatic step of endogenous creatine synthesis via the enzyme AGAT, and this capacity progressively declines with advancing CKD, becoming virtually absent in dialysis-dependent patients [6,86]. Simultaneously, dialysis removes creatine from the body through direct losses into the dialysate, and increasing recommendations towards plant-based diets in CKD further limit exogenous creatine intake [86]. Skeletal muscle biopsies in patients with CKD have demonstrated significantly reduced ATP and phosphocreatine concentrations, and ^{31}P-NMR spectroscopy studies have confirmed decreased phosphocreatine stores in both the heart and skeletal muscle of dialysis patients [86]. The resulting creatine deficiency may substantially contribute to the sarcopenia, fatigue, cognitive impairment, and reduced quality of life that characterise advanced CKD — symptoms strikingly similar to those observed in patients with genetic creatine synthesis deficiencies [6,86]. Available small clinical trials in dialysis patients have demonstrated a 60% reduction in muscle cramp frequency and improvements in lean body mass and malnutrition-inflammation scores following creatine supplementation [86]. These findings justify systematic clinical investigation of creatine as a conditionally essential nutrient in CKD [6,86].

8. Special Populations.

8.1. Chronic Kidney Disease and Pre-existing Renal Impairment.

Individuals with pre-existing kidney disease — particularly those with significantly reduced glomerular filtration rate — represent the population where the greatest caution is warranted [4,5]. The physiological rise in serum creatinine associated with supplementation may mask or confound the assessment of renal function in these patients, making the use of creatinine-independent biomarkers such as cystatin C, directly measured GFR (e.g., by ^{51}Cr-EDTA clearance), proteinuria, and albuminuria essential for accurate monitoring [5]. Current recommendations advise that individuals with very low GFR should use creatine with particular caution and only under medical supervision, while those with mild to moderate renal impairment should likewise supplement only under medical supervision with regular

monitoring of kidney function [4,5]. Paradoxically, as detailed in section 6.4, patients with advanced CKD or dialysis dependency may actually suffer from creatine deficiency and could potentially benefit from carefully supervised supplementation [6,86].

8.2. Pregnancy and Breastfeeding.

Creatine metabolism undergoes significant changes during pregnancy — maternal creatine demand increases substantially as the developing fetus relies on placental transfer of maternal creatine throughout most of gestation [87,88]. Direct evidence for creatine's critical role in fetal development comes from in vivo ^{1}H-MRS studies of 129 healthy fetal brains, which demonstrated that brain creatine concentration increases significantly with gestational age between 18 and 40 weeks (r^2=0.60; $p<0.0001$), reflecting increasing demands for neuronal bioenergetics during cerebral maturation [89]. Animal studies, particularly in spiny mice and guinea pigs, have consistently demonstrated that maternal creatine supplementation is safe and may confer neuroprotective benefits to the fetus in conditions of perinatal hypoxia, preterm birth, or fetal growth restriction [87,90]. A well-designed guinea pig study using a full-term pregnancy model confirmed that maternal creatine supplementation at 0.3 g/kg/day had no significant impact on gestational weight gain, fetal growth, umbilical blood flow, offspring birthweight, pregnancy length, stillbirth rate, neonatal glucose tolerance, or body composition at 28 days postnatal — providing strong preclinical support for its safety in healthy pregnancies [90].

Despite this promising preclinical evidence, clinical data in humans regarding creatine supplementation during pregnancy remain very limited. The first open-label pharmacokinetic dose-escalation trial conducted in women during the third trimester demonstrated that a single 5 g dose of creatine monohydrate was well tolerated with no major adverse events, and that pharmacokinetic parameters were comparable to non-pregnant women — representing a first step toward establishing a safe dosing regimen in this population, though the study was not designed to evaluate clinical safety or efficacy endpoints [91]. A qualitative study conducted among 42 pregnant women and 100 healthcare professionals in Australia found that women would consider taking creatine if recommended by their clinician, while healthcare professionals would require detailed safety and efficacy data before incorporating creatine into clinical guidelines — indicating readiness within the field to pursue further research while acknowledging that the current evidence base remains insufficient [92].

Randomised controlled trials in pregnant women specifically designed to evaluate the safety and efficacy of creatine supplementation remain absent, and current data are insufficient to support any clinical recommendations regarding creatine use in pregnancy [87,91,93]. Alternative forms of creatine — particularly creatine ethyl ester, which contains ethanol — should be explicitly avoided by pregnant and breastfeeding women [21].

8.3. Children and Adolescents.

Creatine supplementation is widely used among adolescent athletes, with surveys consistently identifying it as one of the most commonly consumed performance-enhancing supplements in this demographic [94]. Despite concerns raised in popular media and some scientific literature — where creatine use in adolescents has been inappropriately equated with anabolic drug use without scientific basis — the available evidence does not support these concerns [94]. Multiple studies in adolescent clinical populations, including those with muscular dystrophies, traumatic brain injury, and neuromuscular diseases, have reported no adverse events and no clinically relevant changes in laboratory markers of kidney or liver function [94,95,96]. The United States Food and Drug Administration has designated creatine monohydrate as GRAS, a classification that explicitly extends to older children and adolescents, a position reinforced by a recent expert consensus statement affirming creatine's safety across the lifespan including paediatric populations [79,80,81,94].

However, the evidence base for safety in healthy children and adolescents remains very limited. An independent PRISMA-compliant scoping review encompassing 13 studies with a total of 268 participants aged 11.5–18.2 years, conducted without industry funding, found that no study was designed to assess the safety of supplementation, and findings regarding improvements in athletic performance were inconsistent [97]. The review's authors highlight that the long-term impact of artificially increased muscle mass during physiological growth on joint mechanics, central stabilisation, and musculoskeletal development remains unknown — a unique risk absent in adult populations [97]. Current ISSN guidelines recommend that creatine supplementation in young athletes may be considered appropriate when the athlete is involved in serious supervised training, consuming a well-balanced diet, knowledgeable about appropriate use, and does not exceed recommended dosages [80,94]. Routine supplementation in healthy children and adolescents who do not meet these criteria is not supported by current evidence [97]

8.4. Psychiatric Disorders.

As discussed in section 6.4, creatine supplementation shows promising adjunctive effects in the treatment of unipolar depression; however, patients with bipolar affective disorder represent a population requiring particular caution. Although the total number of documented cases remains small, the safety signal is consistent and derives from two independent studies. Toniolo et al. observed a manic or hypomanic switch in 2 of 35 patients with bipolar depression (5.7%) receiving adjunctive creatine, while Roitman et al. observed switching in both bipolar patients included in their study, with no such events occurring among the unipolar participants [49,50]. The proposed mechanism involves creatine's capacity to increase brain energy availability, which may exacerbate the elevated neuronal excitability characteristic of manic episodes. Patients with a confirmed history of mania or bipolar disorder should therefore be considered at elevated risk, and creatine supplementation in this population should only be undertaken under close psychiatric supervision with careful monitoring for mood destabilisation [49,50].

8.5. Drug Interactions.

Although creatine has limited direct pharmacokinetic interactions with most medications, several clinically relevant considerations deserve attention. The most important relates to the confounding effect of creatine supplementation on eGFR calculations — medications whose dosing is adjusted based on estimated glomerular filtration rate calculated from serum creatinine, such as metformin, certain aminoglycoside antibiotics, and nephrotoxic agents, may require reassessment of dosing strategies in creatine users, as eGFR calculated from serum creatinine may underestimate true renal function [5].

A clinically significant and underappreciated mechanism is the inhibition of renal organic transporters by commonly prescribed medications, leading to increases in serum creatinine independent of renal injury. Physiologically-based pharmacokinetic modelling has demonstrated that trimethoprim, cimetidine, and famotidine inhibit the OCT2 and MATE transporters responsible for active tubular secretion of creatinine in the proximal tubule, producing serum creatinine increases of 7–33% without actual impairment of glomerular filtration [98]. In patients with CKD, this effect may be more pronounced than in healthy individuals due to altered renal transporter activity [98]. This phenomenon carries important clinical implications — it may be misinterpreted as deterioration of renal function and lead to unwarranted discontinuation of treatment.

Cyclosporine has been shown to inhibit the creatine transporter in vitro by altering its surface expression, which may exacerbate nephrotoxicity and explain reported cases of nephropathy in patients concurrently using creatine and cyclosporine [82]. Concomitant use of creatine with nephrotoxic medications — including NSAIDs, cyclosporine, or aminoglycosides — warrants particular caution, especially in populations with pre-existing renal vulnerability [4,5]. Healthcare providers should be informed of creatine use when prescribing medications whose safety monitoring relies on serum creatinine or eGFR, and creatinine-independent markers of renal function should be used where possible [5,98].

Data on creatine's interactions with other drug categories remain limited, and this area is poorly characterised by controlled clinical research. It should nonetheless be noted that creatine may theoretically compete for renal tubular transport with medications eliminated via the same organic transporter systems, which could affect their renal clearance [82].

8.6. Quality and Purity of Supplements.

A frequently overlooked safety consideration is the quality and purity of commercially available creatine products. Studies have documented the presence of contaminants — including heavy metals, dicyandiamide, and dihydrotriazines — in lower-quality supplement formulations [5,52]. These contaminants, rather than creatine itself, may be responsible for some of the adverse events reported in case studies [5]. Consumers are therefore strongly advised to select creatine monohydrate products that have undergone independent third-party testing and certification, and to avoid alternative creatine formulations — particularly creatine ethyl ester — whose safety profiles are substantially less well-characterised than that of creatine monohydrate [5,52].

9. Conclusions.

Creatine monohydrate is one of the most extensively studied dietary supplements in the history of nutritional science, and one of the most unjustly pigeonholed. This narrative review set out to answer the question posed in its title — is creatine only for athletes? The available evidence indicates it is not.

Creatine's biochemical role as the primary substrate of the ATP-phosphocreatine energy buffering system places it at the intersection of virtually every energy-demanding process in the human body — from skeletal muscle contraction during maximal effort, to neuronal firing in the prefrontal cortex, to myocardial contractility [2,3,9]. This pleiotropic nature is what

makes creatine scientifically interesting not only from a sports perspective, but above all from a clinical one. In sport, the evidence base is mature and compelling — creatine supplementation combined with resistance training consistently improves muscle strength, power output, and lean body mass, with the strongest effects in younger and previously untrained individuals, though with clinically meaningful benefits in older populations as well [13,14,15]. In endurance sports the picture is more nuanced — creatine does not improve maximal aerobic capacity, but may benefit athletes in disciplines requiring repeated surges in intensity and rapid glycogen resynthesis [13,17].

The most important conclusion of this review is, however, that creatine has documented or promising applications in several distinct clinical areas, with varying degrees of evidential strength.

The most robustly documented clinical application remains the treatment of skeletal muscle diseases. In muscular dystrophies and inflammatory myopathies, a Cochrane systematic review encompassing multiple randomised controlled trials confirms improvements in muscle strength and functional performance with a good tolerability profile [34]. Among all the clinical applications reviewed here, the available evidence in this area is the strongest to date [34].

In the context of an ageing population, creatine stands out as one of the few supplements with documented effects on both sarcopenia and cognitive function simultaneously. Meta-analyses confirm that creatine combined with resistance training significantly increases lean body mass and muscle strength in older adults, reducing the risk of falls and functional decline [29,31,33]. In parallel, by increasing phosphocreatine availability in the brain, creatine demonstrates pro-cognitive effects particularly pronounced in older individuals, vegans, and under conditions of metabolic stress [8]. Evidence further suggests that the age-related decline in muscular power — termed powerpenia — which occurs earlier than strength loss and has a greater impact on fall risk, may represent a particularly responsive target for creatine combined with high-velocity resistance training [8]. Its action through the muscle-brain axis, including augmentation of BDNF secretion, makes creatine a particularly attractive candidate for multimodal healthy ageing interventions [8,11].

In psychiatry, early clinical data position creatine as a promising adjunct in the treatment of depression. Randomised controlled trials have demonstrated large effect sizes when creatine is used as an add-on to SSRIs in women with major depressive disorder, and a more recent trial confirmed its efficacy as a supplement to cognitive-behavioural therapy in a mixed-gender population [40,43,45]. The mechanistic rationale grounded in prefrontal cortex bioenergetics is biologically plausible, though the scale of available trials remains limited and replication in

large multicentre studies is needed [43]. It should be noted that in patients with bipolar affective disorder, manic switching has been reported in two independent studies — the safety signal is consistent and warrants particular caution in this subgroup [49,50].

In traumatic brain injury, the mechanistic case for creatine as a neuroprotective agent is compelling — creatine reduces mitochondrial damage, lowers reactive oxygen species production, and stabilises neuronal membrane potential under hypoxic conditions [27]. Clinical evidence in humans is to date best documented in paediatric populations, where the randomised clinical trial by Sakellaris et al. demonstrated improvements in cognitive outcomes and reduced post-injury complications [27,28,96]. Data in adults are methodologically weaker and require replication in large randomised trials.

In type 2 diabetes, creatine exerts a mechanistically distinct effect on insulin sensitivity through AMPK activation and upregulation of GLUT-4 expression [57,58]. Combining creatine with resistance training yields additional metabolic benefits compared with training alone in diabetic patients [53,61], though the heterogeneity of available studies precludes formal clinical recommendations [60]. Noteworthy is the clinical intersection between type 2 diabetes and sarcopenia — both conditions create a mutually reinforcing metabolic and musculoskeletal vicious cycle, and creatine may address both simultaneously through complementary mechanisms [8,53].

In oncology, the picture is complex and requires honest appraisal. Preclinical data point to a dual role for creatine — potential enhancement of antitumour immunity through CD8+ T cell bioenergetics and synergy with immune checkpoint blockade [69], alongside the observation that in some orthotopic models creatine may promote invasion and metastasis through the Smad2/3 pathway [70] — this fundamental ambiguity must be taken into account when designing further research. Clinical data on cancer cachexia are generally negative or inconclusive — a systematic review of seven trials with 463 participants found no significant between-group differences in body composition [71], and the largest RCT with 263 patients showed no benefit on any endpoint [73]. The immunometabolic potential of creatine in combination with cancer immunotherapy remains a fascinating but purely preclinical hypothesis requiring investigation in human trials.

Regarding pregnancy, emerging data are preliminarily encouraging — the first pharmacokinetic trial in women during the third trimester demonstrated good tolerability and pharmacokinetics comparable to non-pregnant women, and the documented increase in fetal brain creatine concentration between 18 and 40 weeks of gestation confirms its biological relevance to fetal neurodevelopment [89,91]. Nevertheless, randomised controlled trials specifically designed to

evaluate the safety and efficacy of creatine supplementation in human pregnancy remain absent, and formal clinical recommendations are premature [87,91,93].

Across all the clinical areas reviewed, the same pattern emerges — preclinical and mechanistic evidence is often strong, early human trials are sometimes encouraging, but large, well-designed, long-term randomised controlled trials in specific clinical populations remain scarce. What is most needed are studies with adequately long follow-up periods, standardised dosing protocols, and clinically meaningful endpoints such as functional capacity and quality of life rather than body composition parameters alone [8,15,33,71,72]. Heterogeneity in dosing protocols, supplementation duration, and population characteristics further limits the ability to draw firm conclusions across many of the applications reviewed [8,14,15].

On the question of safety, the conclusions are reassuring. Creatine monohydrate does not cause kidney damage in healthy individuals — the observed rise in serum creatinine is a metabolic artefact rather than a marker of pathology [5,83]. It is worth noting that patients with advanced chronic kidney disease may, contrary to widespread belief, suffer from creatine deficiency resulting from impaired endogenous synthesis and dialysis-related losses [6,86]. Hepatic safety data are equally reassuring [5,79,85]. The safety profile extends across age groups, though individuals with advanced CKD, bipolar affective disorder, pregnant women, and children require individualised clinical assessment [4,5,6,49,50,87,93,94]. It should also be noted that despite the widespread use of creatine among adolescents, studies specifically designed to assess the safety of supplementation in this age group are absent — a meaningful gap that warrants attention [97]. Creatine monohydrate remains the gold standard — no alternative form has demonstrated superiority in well-controlled trials, and selecting products with independent third-party quality certification minimises the risk associated with contaminants [2,5,52,80].

Creatine is not only for athletes. It is a molecule with fundamental roles in cellular energy homeostasis, a thirty-year safety record in healthy populations, and a growing body of evidence supporting real benefits in selected clinical conditions, with evidence of varying strength. Its accessibility, affordability, and tolerability make it one of the most promising candidates for broader integration into clinical practice — provided that the research community rises to the challenge of generating the high-quality evidence that such integration demands.

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