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Creatine Supplementation for Dementia Prevention: A Narrative Review

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Abstract

Purpose: The primary objective of this narrative review is to evaluate contemporary scientific evidence regarding the efficacy of oral creatine monohydrate supplementation in the prevention and mitigation of cognitive decline and dementia [23, 17].

Research materials and methods: A systematic search of academic databases, including PubMed, Scopus, and Google Scholar, was conducted to analyze peer-reviewed literature, randomized controlled trials, meta-analyses, and preclinical models focusing on brain bioenergetics and neurodegeneration [3, 23].

Basic results: Results indicate that the brain consumes approximately 20% of resting energy, necessitating efficient ATP regeneration via the phosphocreatine-creatine kinase system [11, 24, 21]. Oral supplementation increases brain creatine levels by 3–10%, potentially narrowing the bioenergetic gap associated with neurodegeneration [20, 11, 18]. Clinical findings demonstrate

significant improvements in memory performance, particularly in adults aged 66–76 years and those under metabolic stress [8, 3, 22]. Preclinical models further suggest that creatine mitigates amyloid- β neurotoxicity and enhances spatial memory by upregulating markers of synaptic plasticity [16, 9, 26].

Conclusions: Creatine is a safe, accessible intervention that supports brain metabolism and neuroprotection [13, 21]. Preliminary evidence positions creatine as a promising adjunctive therapy for dementia prevention, although future long-term clinical trials are essential to establish optimal dosing protocols [10, 9, 23].

Key words: creatine; dementia; Alzheimer's disease; brain health; cognitive function.

1. Introduction

The human brain is a uniquely demanding organ from a metabolic perspective. Despite representing only approximately two percent of total body mass, it is responsible for roughly twenty percent of the body's resting energy consumption [11, 18, 24]. This extraordinary energy expenditure is required to support critical cellular processes, including the maintenance of ionic gradients across neuronal membranes, the exocytosis of neurotransmitters, and the high-frequency signaling activities of synapses [11, 21, 24]. Because adenosine triphosphate (ATP) cannot be stored in significant quantities within neurons, the brain relies on highly efficient regeneration systems to maintain its functional stability [11, 24, 25].

Creatine (Cr), a nitrogenous organic acid obtained through dietary sources like red meat and seafood or via endogenous synthesis in the liver, kidneys, and brain, serves as a primary temporal and spatial buffer in this energy metabolism [1, 5, 11, 21]. Through a reversible reaction catalyzed by the brain-specific isoform of the enzyme creatine kinase (BB-CK), creatine facilitates the rapid regeneration of ATP from adenosine diphosphate (ADP) using stored phosphocreatine (PCr) [9, 21, 24]. This phosphocreatine-creatine kinase shuttle is capable of resynthesizing ATP significantly faster than both oxidative phosphorylation and glycolytic processes, providing an evolutionary advantage for tissues with high and fluctuating energy demands [11, 21, 24].

In the context of healthy aging and neurodegeneration, the efficiency of this system is often compromised. Conditions such as Alzheimer's disease (AD) and other forms of dementia are characterized by bioenergetic failure, which frequently involves mitochondrial dysfunction and impaired glucose utilization that precede clinical symptoms [9, 10, 18]. As energy demand increasingly exceeds supply, the CK/PCr system becomes critical for maintaining neuronal viability and delaying the onset of energetic failure [9, 11, 17]. Furthermore, research suggests

that total brain creatine levels may decline with age, creating a "metabolic gap" that may be bridged through exogenous supplementation [12, 13, 21].

Research Objective. The primary objective of this narrative review is to synthesize and critically evaluate contemporary scientific evidence regarding the role of oral creatine monohydrate supplementation as a neuroprotective strategy for dementia prevention and the mitigation of cognitive decline.

Review Questions.

1. Does oral creatine monohydrate supplementation significantly increase total brain creatine and phosphocreatine levels in aging adults across different brain regions? [20, 21]
2. Which specific cognitive domains—such as memory, executive function, or processing speed—are most effectively augmented by creatine supplementation in the context of age-related neuroatrophy? [8, 13, 24]
3. What is the current scientific evidence for creatine's ability to modulate pathological biomarkers of Alzheimer's disease, including amyloid- β toxicity and tau phosphorylation? [9, 16, 26]

2. Research materials and methods

2.1. Procedure The methodology of this narrative review involved a comprehensive and systematic evaluation of the current scientific literature to identify pertinent studies investigating the role of creatine in brain health and neurodegeneration. A rigorous search was conducted across leading electronic databases, including PubMed/MEDLINE, Scopus, Web of Science, the Cochrane Library, and Google Scholar [3, 8, 13, 17, 23, 24]. To ensure a thorough synthesis, the search strategy utilized a combination of Medical Subject Headings (MeSH) and specific keywords, such as "creatine supplementation," "creatine monohydrate," "dementia," "Alzheimer's disease," "cognitive function," "brain bioenergetics," "neuroprotection," and "aging" [3, 8, 9, 17, 23, 24]. Boolean operators (AND, OR) were employed to refine the search and maximize the retrieval of relevant records [3, 13]. The bibliography search and article selection were finalized in February 2026, covering literature published from 1993 through 2026 to capture both foundational findings and the most contemporary clinical developments [3, 23].

2.2. Inclusion and Exclusion Criteria To maintain high academic standards, this review prioritized peer-reviewed original research, particularly randomized controlled trials (RCTs), systematic reviews, and meta-analyses involving human participants [3, 8, 13]. Specific

attention was given to studies involving older adults (aged 55+ years) and clinical populations with existing cognitive impairments [8, 13]. Furthermore, high-quality preclinical animal models, such as those utilizing 3xTg-AD mice or lipopolysaccharide (LPS)-induced cognitive deficit models, were included to provide insights into the biomolecular and cellular mechanisms of creatine that cannot be easily measured in vivo in humans [9, 16, 26]. Studies were excluded if they focused on non-monohydrate forms of creatine, lacked a clear assessment of cognitive function, or were not available in English or Polish [1, 13, 23].

3. Literature Synthesis

3.1. Participants

The cohort of participants analyzed in this narrative review represents a broad demographic and clinical spectrum, facilitating a multifaceted evaluation of creatine's efficacy across various biological states and energy requirements. A primary focus of the synthesis is placed on older adults aged fifty-five years and older, a population group increasingly vulnerable to age-related declines in brain bioenergetics and the development of a "metabolic gap" that exogenous creatine is hypothesized to bridge [13, 8]. Within this demographic, the review incorporates evidence from healthy community-dwelling seniors as well as sedentary individuals who were medically cleared to participate in high-load resistance training interventions [2, 13]. Furthermore, the review evaluates data derived from healthy volunteers, including young adults (typically aged eighteen to thirty-one) and specialized subgroups such as vegetarians and vegans [7, 15, 23]. These populations are of particular interest because their lower dietary intake of creatine from animal products often results in lower baseline tissue levels, potentially making them more responsive to supplemental monohydrate [7, 15, 24]. Crucially, to address the therapeutic potential of creatine, this work integrates findings from clinical populations with cognitive impairment. This includes individuals diagnosed with Mild Cognitive Impairment (MCI), Parkinson's disease, and Alzheimer's disease (AD), as well as those with fibromyalgia and chronic schizophrenia [3, 9, 17]. Stringent inclusion and exclusion criteria were applied across the cited trials; for instance, many studies required specific Mini-Mental State Examination (MMSE) scores (e.g., ≥ 17 or ≥ 23) to accurately classify the severity of cognitive decline and ensure the safety of participants during metabolic or physical testing [6, 10, 25]. The inclusion of both males and females across these diverse groups allows for the exploration of sex-specific neuroprotective responses to creatine supplementation [2, 9, 25].

3.2. Brain Creatine Uptake and Bioenergetics

The maintenance of cerebral energy homeostasis is an intricate process, given that neurons lack significant ATP storage capacity and require a constant supply of energy to support cellular processes such as neurotransmitter exocytosis and the maintenance of ionic gradients [11, 18, 24]. Creatine (Cr) serves as a vital temporal and spatial high-energy phosphate-storage buffer, facilitating the rapid regeneration of ATP from ADP via the reversible creatine kinase (CK) reaction [1, 9, 11, 21]. In the central nervous system, this is primarily mediated by the brain-specific isoform, BB-CK, which operates at a rate significantly exceeding both oxidative phosphorylation and anaerobic glycolysis, thereby ensuring metabolic stability during fluctuations in energy turnover [9, 11, 24].

The human brain secures its creatine supply through a dual-source mechanism: endogenous synthesis and uptake from peripheral circulation [9, 11, 21, 24]. Endogenous synthesis involves a two-step enzymatic process initiated by the transfer of an amidino group from L-arginine to glycine to form guanidinoacetate (GAA), a reaction catalyzed by L-arginine:glycine amidinotransferase (AGAT). Subsequently, GAA is methylated to form creatine by guanidinoacetate N-methyltransferase (GAMT) [5, 9, 11, 21]. These enzymes are expressed widely across various cell types in the brain, including astrocytes and oligodendrocytes, suggesting that brain creatine levels can be maintained partially independently of dietary intake [9, 11, 24].

Peripheral creatine enters the brain by crossing the blood-brain barrier (BBB) via the sodium- and chloride-dependent creatine transporter (CRT1/SLC6A8) [9, 11, 21, 24]. However, the efficiency of this uptake is significantly lower than that observed in skeletal muscle [11, 24]. This resistance to peripheral uptake is attributed to the limited expression of SLC6A8 in the microcapillary endothelial cells of the BBB and its apparent absence in astrocytes, which may limit the entry of exogenous creatine into the brain parenchyma [11, 21, 24]. Consequently, while skeletal muscle creatine levels can increase by twenty to forty percent with standard supplementation, the brain likely requires higher doses and longer durations of intake to achieve meaningful elevations [11, 21].

Quantitative localized proton magnetic resonance spectroscopy (¹H-MRS) has demonstrated that oral supplementation with high-purity creatine monohydrate can increase total brain creatine content by approximately three point five percent to thirteen point three percent, with most studies reporting an average increase of five to ten percent [20, 11, 21, 24]. These increases are regionally dependent; for instance, significant elevations have been recorded in the gray matter (four point seven percent), white matter (eleven point five percent), and cerebellum (five

point four percent), with the most pronounced augmentation observed in the thalamus (fourteen point six percent) [20, 11]. This augmentation of the cerebral creatine pool facilitates energy stability during periods of high demand, effectively delaying the onset of energetic failure [9, 11, 24]. In the context of Alzheimer's disease, where mitochondrial dysfunction and reduced glucose utilization serve as early pathological hallmarks, preserving the phosphocreatine/ATP ratio through supplementation represents a critical neuroprotective strategy to prevent downstream neuronal apoptosis and cognitive degradation [9, 10, 18, 22].

3.3. Cognitive Effects in Aging

The impact of aging on cognitive processes is closely linked to a progressive decline in cerebral bioenergetics and a potential reduction in total brain creatine content [11, 21]. Comprehensive meta-analytical data suggest that exogenous creatine monohydrate supplementation is a potent strategy to counteract these deficits, demonstrating a significant positive effect on overall memory performance with a standardized mean difference (SMD) ranging from zero point twenty-nine to zero point thirty-one [8, 3]. Subgroup analyses further clarify that these benefits are highly age-dependent; while effects in younger populations are often negligible under non-stressed conditions, the most robust clinical improvements are consistently observed in older adults aged between sixty-six and seventy-six years, where the effect size has been reported to reach zero point eighty-eight [8, 3, 23].

Specific dosing protocols, such as high-dose loading (typically twenty grams per day for five to seven days), have proven particularly effective in clinical trials involving healthy community-dwelling seniors [8, 21, 23]. This regimen has been shown to yield measurable enhancements in various memory domains, including forward number recall, long-term memory, and both forward and backward spatial recall [8, 21, 24]. These improvements are attributed to creatine's role as a temporal and spatial energy buffer that sustains adenosine triphosphate (ATP) levels during demanding cognitive tasks, thereby bridging the "metabolic gap" that occurs when energy demand exceeds supply in the aging brain [9, 11, 18].

Beyond isolated supplementation, the integration of creatine with physical activity represents a synergistic approach to preserving brain health and promoting neuroprotection. Combining daily creatine intake (e.g., three grams per day) with high-load, velocity-intentional variable resistance training has been shown to induce significant biological adaptations in older adults, including improved neurocognitive performance and favorable changes in neuroplasticity biomarkers [2, 13]. Mechanistically, this combination may enhance neuroplasticity by facilitating the upregulation of brain-derived neurotrophic factor (BDNF) through muscle-brain

crosstalk and potentially stimulating the mTORC1 signaling pathway, both of which are essential for synaptic stability and the formation of new memories [2, 9, 26]. Furthermore, evidence indicates that such multimodal interventions not only support memory and attention but also translate into meaningful improvements in neuromuscular strength, physical function, and overall health-related quality of life in the elderly [2, 13, 23].

Table 1. Summary of key clinical trials evaluating creatine supplementation and cognitive function in older adults.

Study (Author, Year)	N (Participants)	Dose	Duration	Main Findings
McMorris et al. (2007) [8]	32 (Healthy seniors, avg. 76 yrs)	20 g/day (4 x 5g)	7 days	Significant improvement in forward number recall, long-term memory, and spatial recall tasks.
Rawson et al. (2008) [11]	32 (Older adults, 60–82 yrs)	20 g/day (loading) + 5 g/day	4 weeks	No significant effect on memory (digit span) or executive function in healthy, non-stressed seniors.
Alves et al. (2013) [25]	41 (Older women, avg. 67 yrs)	5 g/day	12 weeks	No significant changes in cognitive performance (MMSE, Verbal Fluency) even when combined with resistance training.
Smolarek et al. (2020) [11, 13]	33 (Healthy seniors)	5 g/day	12 weeks	Combined with resistance training, led to improved cognitive screening scores and neuromuscular function.

3.3.1 The SLC6A8 Bottleneck: The Primary Conflict in Brain Supplementation

The most significant challenge to the efficacy of oral creatine supplementation in neuroprotection is the existence of a physiological bottleneck at the blood-brain barrier (BBB) [4, 11, 24]. While skeletal muscle lacks the capacity for endogenous creatine synthesis and relies entirely on uptake from circulation via the sodium- and chloride-dependent creatine transporter (SLC6A8/CRT1), the brain maintains a more autonomous but restricted system [5, 11, 21].

Transporter Distribution and Expression. SLC6A8 is a member of the solute carrier family 6 and is expressed on the microcapillary endothelial cells that form the BBB [5, 11, 14].

However, contemporary evidence highlights three critical factors that make brain uptake significantly more difficult than muscle uptake:

1. **Limited Density:** SLC6A8 is not an abundant component of the BBB capillaries, which inherently limits the rate at which peripheral creatine can enter the central nervous system [4, 11].
2. **Astrocyte Absence:** Research suggests that while neurons and oligodendrocytes express the transporter, astrocytes (which are integral to the BBB structure) appear to lack SLC6A8 expression [11, 14, 21]. This absence creates a significant barrier for the entry of exogenous creatine into the brain parenchyma [11, 21, 24].
3. **Downregulation Mechanisms:** Prolonged exogenous creatine intake has been shown to potentially downregulate the expression of the SLC6A8 transporter, which may lead to a plateau or "resistance" to the supplement over time [4, 11].

The Bioenergetic Conflict. This restricted permeability explains why skeletal muscle creatine levels can increase by up to forty percent with standard dosing, whereas the brain typically exhibits a much more modest increase of only three to ten percent [11, 20, 21]. This discrepancy is the core of the academic controversy: some researchers argue that the brain is largely refractory to oral supplementation unless metabolic status is severely compromised [8, 11, 14]. Conversely, individuals with Cerebral Creatine Deficiency Syndromes (CCDS)—specifically those with mutations in the SLC6A8 gene—demonstrate that when the transporter is non-functional, the brain cannot compensate through endogenous synthesis alone, leading to profound cognitive disability that is, unfortunately, unresponsive to oral creatine because the entry gate is permanently closed [9, 16, 11].

Strategies for Overcoming the Barrier. To bypass the SLC6A8 bottleneck, clinical researchers are investigating higher dosing protocols (e.g., twenty grams per day for multiple weeks) and alternative energy precursors [4, 10, 11]. One promising alternative is guanidinoacetic acid (GAA), the immediate precursor to creatine. Unlike creatine, GAA appears to utilize additional transport routes—such as SLC6A6 (taurine transporter) and GAT2 (GABA transporter)—and can achieve up to a sixteen percent increase in brain creatine levels, effectively bypassing the primary SLC6A8 conflict [11, 14, 24].

In the context of dementia prevention, the "SLC6A8 conflict" suggests that standard athletic doses (three to five grams) may be insufficient to narrow the bioenergetic gap in the aging brain. Successful neuroprotection likely requires sustained, higher-dose strategies to facilitate even the modest three-to-ten-percent increase necessary to stabilize neuronal ATP during metabolic stress [9, 11, 21].

3.4. Neuroprotection and Alzheimer's Disease

Alzheimer's disease is increasingly recognized not only as a proteinopathic condition but also as a disorder characterized by profound bioenergetic failure. A primary pathological hallmark of AD is mitochondrial dysfunction and a significant reduction in cerebral glucose utilization, both of which typically manifest and progress decades prior to the clinical emergence of symptomatic dementia [9, 10, 18, 25]. This metabolic impairment leads to a critical decline in adenosine triphosphate (ATP) levels within hippocampal and cortical neurons [9, 10]. Because cellular survival is strictly dependent on ATP homeostasis, this energetic deficit is hypothesized to be a key upstream contributor to the accumulation of amyloid- β (A β) plaques and the subsequent cascade of neuronal apoptosis [9, 10, 25].

In advanced preclinical models of neurodegeneration, chronic dietary creatine supplementation has demonstrated substantial neuroprotective efficacy. Research utilizing the 3xTg-AD transgenic mouse model—which expresses both A β plaques and tau neurofibrillary tangles—shows that oral intake of creatine (three percent by weight) leads to a significant enhancement of hippocampal-dependent spatial memory and improved learning rates [9, 16, 21]. These behavioral gains are accompanied by a robust upregulation of synaptic plasticity-related proteins, including postsynaptic density protein-95 (PSD-95) and calcium/calmodulin-dependent protein kinase II (CaMKII), particularly in the hippocampus [16, 26]. Mechanistically, these effects are linked to the modulation of the NF- κ B transcription factor complex; by downregulating the inhibitor protein I κ B, creatine facilitates the activation of signaling pathways essential for synaptogenesis and neuronal stability [16, 21].

Furthermore, creatine appears to possess the unique capacity to directly modulate the classic pathological biomarkers associated with AD progression. Preclinical evidence indicates that creatine can inhibit amyloid- β neurotoxicity by providing a superior energy buffer (increasing the PCr/ATP ratio), which preserves mitochondrial membrane integrity even in the presence of toxic peptides [9, 16, 22]. In female AD models, supplemental creatine has been shown to alter amyloidogenic processing by upregulating high-molecular weight A β species while downregulating the more toxic low-molecular weight oligomers [9]. Additionally, increased hippocampal creatine concentrations have been correlated with a reduction in the ratio of phosphorylated tau to total tau (pTau/Tau) across both sexes [9].

Beyond its bioenergetic role, creatine exerts a potent influence on neuroinflammation and oxidative stress, both of which are central to the pathogenesis of AD and mild cognitive impairment (MCI). Creatine has been shown to ameliorate cognitive deficits induced by lipopolysaccharide (LPS)—a common model for neuroinflammation—through the activation

of the mTORC1 signaling pathway and the subsequent upregulation of synaptic proteins in the dentate gyrus [9, 17, 26]. It also functions as an indirect antioxidant by supporting mitochondrial efficiency and potentially scavenging reactive oxygen species (ROS) [9, 21]. While clinical trials in humans with AD are still in their infancy, the ongoing CABA trial represents a critical milestone, investigating whether high-dose creatine monohydrate (twenty grams per day) can effectively alter brain metabolite concentrations and improve cognitive outcomes in patients already diagnosed with the disease [9, 10].

4. Discussion

The findings synthesized in this narrative review underscore a critical relationship between cerebral energy metabolism and the preservation of cognitive integrity during the aging process. Aging is inherently characterized by a progressive deterioration of physiological functions, prominently involving a decline in mitochondrial respiratory efficiency and a subsequent reduction in cellular oxygen consumption [18, 13]. The human brain, a uniquely metabolically active organ requiring approximately twenty percent of the total resting energy of the body, is particularly susceptible to these disruptions [11, 24]. This creates a "bioenergetic gap" or "metabolic gap," where mitochondrial decay—marked by reduced membrane potential and impaired oxidative phosphorylation—leads to a chronic deficit in adenosine triphosphate (ATP) production [9, 18, 24, 13]. In conditions such as Alzheimer's disease (AD) and mild cognitive impairment (MCI), this bioenergetic failure often precedes the histological and clinical manifestation of symptoms, triggering a cascade of oxidative stress, mitochondrial DNA damage, and eventually, the failure of neuronal ion-transport systems [9, 10, 18].

The evidence presented herein strongly supports the metabolic hypothesis of neuroprotection, which posits that interventions aimed at sustaining ATP levels can improve neuronal dysfunction and mitigate cell loss [9, 11, 18]. Creatine serves as a critical spatial and temporal buffer in the central nervous system by facilitating the rapid regeneration of ATP from adenosine diphosphate (ADP) via the reaction catalyzed by the brain-specific isoform of creatine kinase (BB-CK) [9, 11, 21, 24]. By elevating the phosphocreatine (PCr) to ATP ratio, supplemental creatine provides a robust and rapidly accessible energy reserve that sustains essential cellular processes—such as neurotransmitter exocytosis and the maintenance of membrane potentials—even under conditions of high metabolic demand or hypoxic stress [11, 21, 24, 22]. Furthermore, creatine exerts both direct and indirect antioxidant effects; it can scavenge reactive oxygen species (ROS) and stabilize mitochondrial membranes, thereby inhibiting the activation

of pro-apoptotic signaling pathways and preventing neuronal death induced by amyloid- β toxicity [9, 11, 21, 16].

However, the clinical application of creatine for dementia prevention must account for the distinct pharmacological barriers inherent to the central nervous system. A central observation in current research is that brain uptake of creatine is significantly slower and more restricted than uptake in skeletal muscle [11, 21, 24]. This resistance to peripheral uptake is primarily attributed to the limited expression of the sodium- and chloride-dependent creatine transporter (SLC6A8/CRT1) within the microcapillary endothelial cells of the blood-brain barrier [11, 21, 24, 9]. Quantitative localized proton magnetic resonance spectroscopy (1H-MRS) has demonstrated that while skeletal muscle can increase total creatine content by twenty to forty percent, the human brain typically exhibits more modest elevations ranging from three to ten percent [11, 20, 21, 24]. These regional increases are also non-uniform, with the most pronounced augmentation often observed in the thalamus [20, 11].

Consequently, the "bioenergetic gap" of the aging brain likely necessitates specialized administration regimens. Evidence suggests that achieving meaningful elevations in cerebral creatine requires longer durations of supplementation (spanning several weeks to months) or higher dosing protocols compared to those used for athletic performance [11, 21, 14]. While short-term loading (e.g., twenty grams per day for seven days) has shown cognitive benefits in seniors, long-term maintenance doses may be required to facilitate persistent ATP stability and counteract the progressive energetic failure characteristic of neurodegenerative diseases [8, 9, 11, 21]. Future investigations, such as the ongoing CABA trial, will be essential in defining the optimal dosing intervals and thresholds required to maximize the neuroprotective potential of creatine monohydrate in clinical populations at risk for dementia [10, 9].

5. Conclusions

Creatine monohydrate supplementation has demonstrated a statistically significant capacity to augment memory performance in older adults, particularly those within the sixty-six to seventy-six-year age bracket [8, 13]. This clinical effect is fundamentally rooted in creatine's ability to act as a temporal and spatial high-energy phosphate buffer, facilitating the rapid regeneration of adenosine triphosphate (ATP) from ADP via the reaction catalyzed by the brain-specific creatine kinase isoform (BB-CK) [11, 24]. By effectively narrowing the bioenergetic or "metabolic gap" characteristic of the aging brain—where mitochondrial respiratory efficiency often declines and tissue creatine levels may decrease—supplemental creatine supports the high metabolic demands required for neurotransmitter exocytosis, synaptic signaling, and the

consolidation of information [9, 11, 13, 18]. Meta-analytic evidence confirms that these cognitive gains are most robust in community-dwelling seniors, suggesting that creatine serves as a potent neuroenergetic aid that preserves functional stability during the aging process [8, 13, 23].

Robust preclinical evidence derived from advanced transgenic animal models suggests that chronic dietary creatine intake can significantly slow the progression of Alzheimer's disease (AD) pathology by mitigating amyloid- β (A β) neurotoxicity and supporting mitochondrial integrity [9, 16]. Specifically, research utilizing the 3xTg-AD mouse model—which expresses the hallmark plaques and neurofibrillary tangles of the disease—has shown that oral creatine supplementation improves hippocampal-dependent spatial memory and learning rates [9, 16, 21]. These behavioral improvements are accompanied by a significant upregulation of essential synaptic plasticity-related proteins, including PSD-95 and CaMKII, as well as the modulation of the NF- κ B transcription factor complex [16, 21]. Furthermore, creatine appears to directly influence hallmark biomarkers of AD by favoring the production of high-molecular weight amyloid species over more toxic low-molecular weight oligomers and reducing the ratio of phosphorylated tau to total tau (pTau/Tau) [9, 16]. In models of neuroinflammation, creatine further ameliorates cognitive deficits through the activation of the mTORC1 signaling pathway in the dentate gyrus, reinforcing its role as a multifaceted neuroprotective agent [9, 26].

Despite the encouraging results observed in healthy seniors and preclinical models, there is an urgent need for large-scale, long-term randomized controlled trials (RCTs) specifically targeting clinical populations with mild cognitive impairment (MCI) and symptomatic dementia [10, 23]. Current human data regarding the therapeutic efficacy of creatine in patients already diagnosed with Alzheimer's disease remain limited, and the heterogeneity of results in younger cohorts suggests that baseline creatine status and task difficulty are critical moderators of success [8, 9, 23]. While pilot investigations such as the CABA study are currently evaluating the feasibility and bioenergetic impact of high-dose creatine (twenty grams per day) in AD patients, future research must prioritize the objective measurement of brain creatine concentrations via magnetic resonance spectroscopy (1H-MRS) [9, 10]. Such studies will be essential to establish optimal dosing protocols and to determine if sustained metabolic support can effectively alter the clinical trajectory of neurodegenerative failure in vulnerable populations [9, 13, 23].

6. Disclosure

Authors' Contributions:

Conceptualization: J.P.

Formal analysis: J.P., M.W., A.S., N.W., J.L., J.Pr., D.K.O., L.R., G.K., J.La., P.K., B.G., O.S.

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