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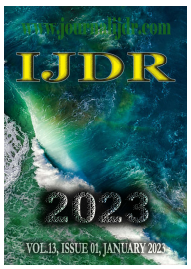

RESEARCH ARTICLE OPEN ACCESS

EFFECTS OF CREATINE SUPPLEMENTATION IN ALZHEIMER'S PATIENTS

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ABSTRACT

Creatine is an amino acid compound present mainly in muscle fibers and in the brain, very important for the process of supplying and depositing intracellular energy. Its antioxidant action offers a therapeutic possibility in neurodegeneration processes, which involve oxidative stress of the nervous system, it has properties that reduce mental fatigue and protect the brain from neurotoxicity. This review addresses the metabolism of creatine and its possible therapeutic interventions in neurological function and the material used includes descriptive articles on the metabolism of the supplement and studies on the progressive decrease of phosphocreatine (PCr) with the advancement of degenerative diseases. In conclusion, creatine is already widely used for sports purposes and muscle performance, but it is evident that its role goes beyond the already known barriers and may have therapeutic values about Alzheimer's. However, the investigation of applicability is still at an early stage and the results are in the process of becoming evident.

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INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative, chronic, progressive disease, in which there is an irreversible disorder in the central nervous system, causing the destruction of neurons that, therefore, characterize cognitive impairments, which include agnosia, apraxia and dysphasia. In addition, it causes changes in the behavior, personality, and mood of the individual [6]. Alzheimer's can affect people from the age of 40, but mostly affects people over 65. WHO estimates indicate that in 2025 there will be about one billion people over 60 years old in the world [7] In Brazil, according to the Brazilian Institute of Geography and Statistics (2019), there are 32.9 million elderly people over the age of 60 and almost two million people have dementia, with about 40 to 60% of them being Alzheimer's. Women are most often affected [20] - [17]. With the increase in life expectancy and the number of elderly people occurring in recent years, it has become essential to monitor pathologies such as dementia and neuropsychiatric disorders, as these accompany the natural aging process. The elderly affected by Alzheimer's have their physical, mental and social integrity compromised, leading to situations of total or partial dependence, often requiring complex care [4].

Faced with the aging process and the emergence of supplements in the contemporary world, new discussions and ideas related to the delay of neurodegenerative diseases such as Alzheimer's have arisen. New uses of creatine supplement have attracted attention suggesting that they may have an important relevance in preventing or delaying the development of these types of age-associated degenerative diseases [21]. Creatine is a supplement for muscle hypertrophy as it is known, however, in the brain, it has been seen to have antioxidant properties that reduce mental fatigue and protect the brain from neurotoxicity, improving certain aspects and improving the prognosis of diseases such as depression and bipolarity [21]. The combination of factors like this makes creatine an excellent candidate for the prevention of neurological diseases related to the aging process, increasing functional reserves and promoting supraphysiological barriers.

METHODS

The research of the bibliographic material was carried out in a few stages. First, the databases were defined, and then the journals PUBmed, Scielo and CAPES to identify the articles, with the

objective of examining the scientific productions that permeate the theme of the benefits of creatine in elderly people affected by Alzheimer's. Subsequently, descriptors were defined in pairs for the search for articles and inclusion criteria, using the "AND" and "OR" operators and other tools. The search was restricted to articles published in Portuguese and English from 1998 to 2015. Finally, a reading of the titles and abstracts of all articles was carried out, in order to select those that addressed the subject of the review, excluding those that fall outside the purpose in question. The inclusion criteria for surveying the articles were the following descriptors in Portuguese and English: Alzheimer's disease, Creatine, Treatment. Such words were combined with each other to culminate in the writing of the results analysis and in their discussion and presentation. In addition to the descriptors, the chosen publications should be between 2009 and 2022, have people with Alzheimer's as subjects of study and creatine supplementation as a possible therapy. As an exclusion criterion, not meeting at least one of the inclusion criteria. Finally, 24 articles were analyzed for proper data collection.

RESULTS

General: Forty potentially relevant articles were found considering the definition of databases and descriptors. After reading the titles and abstracts of the articles, 16 studies were excluded based on the criteria: they did not cover the neuroprotection of creatine; did not highlight creatine metabolism; and/or highlighted only the ergogenic effects. At the last moment, the remaining articles selected as relevant were analyzed and the review was carried out.

Alzheimer: Alzheimer's is a pathology that has no cure and is currently considered a global public health problem. Alzheimer's disease is associated with brain shrinkage and localized loss of neurons, primarily in the hippocampus and basal part of the forebrain. Its progress can be divided into phases whose symptoms vary in intensity. The first phase is called mild, which may show signs such as loss of recent memory (episodic memory), difficulty finding words and making decisions, disorientation in time and space, depressive and aggressive symptoms, and decreased interest in activities and chores [13] - [25]. The second phase considered a moderate phase of the disease, where the individual has difficulty performing activities of daily living, with memory impairment, greater difficulty in speech and expression, behavioral changes (aggressiveness, irritability, restlessness), hallucinations, nocturnal agitation and sleep disorders [12] - [25]. In the severe phase of the disease, the individual is totally dependent. There is a marked decline in memory, difficulty in communication, eating, locomotion with gait instability and loss of sphincter control. Progressively, the individual loses the ability to walk and is restricted to bed in the more advanced stages. Death occurs from cardiopulmonary complications or from infection [13] - [25].

Neurodegeneration occurs through the formation of senile plaques and neurofibrillary tangles, which occurs due to hyperphosphorylation of the Tau protein, leading to less stability of microtubules, thus favoring neuronal death and loss of synapses. Such factors lead to neuronal inflammation and oxidative stress, generating toxicity and intensifying neurodegeneration [08] - [22]. Early diagnosis is of paramount importance. However, studies indicate that it is underdiagnosed in primary care, delaying diagnosis and causing unfavorable outcomes [15]. The diagnosis of Alzheimer's Disease is clinical, made through anamnesis and cognitive or neuropsychological evaluation, such as the MMSE (mini-mental state examination), this test serves to confirm some symptoms resulting from AD, such as temporal orientation and spatial, memory, attention, languages, and constructive skills helping to identify the disease. The Clock Drawing tests, the Verbal Fluency test for categories and the Blessed Dementia Scale are also used in this initial assessment of patients with suspected cognitive impairment [02]. Definitive diagnosis is only possible by neuropathological examination, by observation of senile plaques and neurofibrillary tangles in the brain tissue, as this is only possible after death, imaging tests such as nuclear magnetic resonance or computed tomography of the skull are used. These exams allow the visualization of the hippocampal region, entorhinal cortex, where the most recent neuropathological alterations in the evolutionary process of the disease are presented, where amnesia is the most important manifestation in this initial phase [18] - [02] - [05]. CSF biochemical tests can be used and the decrease in Aβ42 is indicative of the pathology, and together with phosphorylated Tau, as they can monitor the disease even before the onset of cognitive symptoms [18]. However, they should not be used routinely, being indicated for patients with dementia of pre-senile onset (before 65 years of age), atypical presentation or clinical course, communicating hydrocephalus, and any evidence or suspicion of inflammatory or infectious disease of the nervous system center [02] - [05]. The first-choice pharmacological treatment methods are composed of drugs belonging to the second generation of the class of acetylcholinesterase inhibitors (AchE), they act by inhibiting acetylcholinesterase and butyrylcholinesterase, which are enzymes that catalyze acetylcholine such as donepezil, galantamine and rivastigmine and a glutamate (memantine) N-methyl-D-aspartate (NMDA) receptor antagonist used in more severe cases of the disease. These drugs allow a better quality of life for patients with the disease; however, they do not reverse or recover the neuronal loss. Some drugs have been evaluated for their ability to delay or temporarily stop the progression of the disease [09] - [20] - [05]. Intervention methods are indispensable complements to treatment, promoting an improvement in depression and stress. Among the proposed activities are included cognitive rehabilitation, occupational therapy, physical activity, music therapy, art therapy and support groups [05]. Physical exercise, in turn, acts in the preservation and/or cognitive, functional, and physical improvement of these patients, where systematized aerobic activities increase blood flow and neurogenesis, and decrease oxidative stress and possibly reduce amyloid plaques [14].

Fisiopatology of Alzheimer: The presence of neurofibrillary tangles (NFE) and neuritic plaques (NP) is the necessary condition to macroscopically characterize AD, which lead to an irreversible neurodegenerative process with neuroinflammation [23]. The intracellular ENF consist of paired helical filaments, formed from the tau protein, which is a cytosolic protein, found predominantly in neurons, where its main function is to maintain the stability and assembly of microtubules present in the skeletons of axons, and the hyper tau phosphorylation leads to loss of stability and disruption of these microtubules, in addition to resulting in the formation of neurofibrillary tangles. Abnormal Tau hyperphosphorylation is the result of hyperactivation of kinases and hypoactivation of phosphorylases, possibly due to the accumulation of amyloid beta peptide. When hypersensitized, it is able to provoke mobilization of microglia and release of inflammatory cytokines, causing loss of viability and cell death, triggering a phenomenon of toxicity, with subsequent impediment in axonal transport, contributing to the cognitive deficits that characterize dementia [18] - [23]. Interneuron amyloid beta (Aβ) protein deposition can initiate the process of amyloid plaque formation. Aβ originates from the metabolism of the amyloid precursor protein (APP), by the activity of alpha secretase enzymes, which does not generate amyloid beta. Its product is later cleaved by γ-secretase, generating a small, soluble peptide with a biological function. This pathway is called non-amyloidogenic. In the amyloidogenic pathway, APP is cleaved by β-secretase and then by γ-secretase, giving rise to a peptide with a sequence of 40 or 42 amino acids, with characteristics of insolubility and predisposition to aggregate. Studies suggest that Aβ1-42 is the most toxic form of the peptide, which, because it has two more amino acids, has a greater tendency to aggregate, being able to cause changes in cognitive function. Oligomeric conformations disturb synapses and generate glial cell activation and inflammation, as astrocytes excessively release pro-inflammatory molecules and proteases throughout the cortex and as microglia perform phagocytosis, they also release nitric oxide, glutamate and superoxide radicals, which end up injuring more healthy tissue [23] - [10]. The anatomical basis of cholinergic deficiency is atrophy and degeneration of subcortical cholinergic neurons that provide cholinergic innervation to the entire cerebral cortex. This neurotransmitter is especially important as it is most responsible for memory formation and learning. Furthermore, in this

pathology there is destruction not only of cholinergic neurons, but also of cortical and hippocampal cells that receive cholinergic stimuli. However, AD promotes the degeneration of several other neurotransmitter systems, such as serotonin, glutamate and neuropeptides [12]. There is evidence of a genetic component in the development of Alzheimer's disease and one of the predisposing factors for the development of the disease is the existence of apolipoprotein E (ApoE), which is the main glycoprotein that carries cholesterol to the brain and repairs damage to neurons. The APOE-ε4 allele is associated with the risk of cardiovascular disease and contributes to accelerated deposition of beta amyloid protein [23].

The central events in the pathogenesis of AD are oligomerization, accumulation, and deposition of amyloid beta protein in certain brain regions. Aβ protein levels are related to increased production or decreased elimination or both processes. There is evidence that ApoEparticipates in all these processes. The ApoE receptors LDLr and LRP1, bind with APP and modulate its traffic to the interior of the neuron and for cleavage into Aβ protein to occur. The acceleration of APP endocytosis and processing to Aβ, is related to the high rate of endocytosis promoted by the LRP1 receptor, that is, it plays an important role in synaptic transmission and motor function in the CNS [23] The anatomical basis of cholinergic deficiency is atrophy and degeneration of subcortical cholinergic neurons that provide cholinergic innervation to the entire cerebral cortex. This neurotransmitter is especially important as it is most responsible for memory formation and learning. Furthermore, in this pathology there is destruction not only of cholinergic neurons, but also of cortical and hippocampal cells that receive cholinergic stimuli. However, AD promotes the degeneration of several other neurotransmitter systems, such as serotonin, glutamate and neuropeptides [12].

Creatine: Creatine is a natural compound that can be synthesized by the liver, kidneys and pancreas, coming from the amino acids glycine and arginine. Another way to obtain it is through food, with higher concentrations in red meat and seafood. Most of the creatine found in the body is in skeletal muscle, but there are small amounts in the brain, testicles and heart. Its form of presentation can be in phosphocreatine (PCr) or free creatine. However, during physiological metabolism, part of the creatine or PCr is degraded into creatinine and excreted in the urine, requiring daily replacement to maintain normal reserves. Thus, when adding the endogenous production with the intake from food and comparing with the excreted metabolic by-product, a balance is obtained. In principle, the metabolic role of creatine is to bind with the phosphate group to form PCr through the enzymatic reaction of creatine kinase (CK). In this sense, when adenosine triphosphate (ATP) is degraded into adenosine diphosphate (ADP) in physiological metabolism, the PCr molecule can be hydrolyzed, releasing phosphate to carry out an ATP resynthesis. As a result, the molecular availability of ATP is renewed for another energy cycle. Further, another mechanism of action of creatine is the acceleration of energy flow, due to its faster connection between sites of ATP production (in the processes of glycolysis and oxidative phosphorylation). According to research by the National Collegiate Athletic Association (NCAA) in 2014, dietary supplementation with creatine monohydrate is very popular in the practice of sports in various modalities, since the supraphysiological consumption of the nutrient is difficult to access with in natura foods, since, for example, a kilogram of raw meat or salmon provides about 1 to 2 g of creatine.

Furthermore, studies such as the one by Harris et al. and Jones et al. show the metabolic benefits with consumption of 3 to 5 g/day of the substance, depending on the amount of muscle mass present, the values may be higher. Parallel to this, it was proven by Balson [03] that supplementation generates a greater retention of creatine in tissues. Consequently, there is an increase in training performance, especially in resistance training with load, increased recovery, increased anaerobic threshold and greater synthesis of muscle glycogen. Likewise, the benefits in the sports field have attracted research attention to new creatine applications aimed at therapeutic options for various clinical populations. Further, the potential use in creatine synthesis deficiencies, neurodegenerative diseases, ischemic heart diseases, improvement in the quality of aging and benefits in pregnancy were highlighted. It is also noteworthy that several studies investigate the safety of creatine supplementation, with groups of different ages and with a wide spectrum of dosages, presenting only the possible side effect of weight gain.

Creatine and neurodegenerative diseases: Close to 95% of creatine storage is in skeletal muscle and 5% in the brain, kidneys and liver, the most understood portion of its role is in participating in energy generation, more specifically, creatine maintains intracellular levels of ATP, which is regulated by mitochondria. Despite being associated with energy production, mitochondria play an important role in the production of reactive oxygen species, calcium regulation, antioxidant mechanisms and regulation of extracellular glutamate. Thus, according to Smith, it is not surprising that a product responsible for regulating energy and other substances, such as mitochondria, is the object of study in relation to neurodegenerative diseases that result in some mechanism of energy deficit. With age, creatine phosphocreatine decreases by about 8% every decade after age 30. Creatine supplementation increases both phosphocreatine and creatine in athletes aged 10-40 [21]. Still based on Smith's bibliographical review, there was benefit in the general health status in the gain of muscle mass in elderly individuals who used creatine in the form of supplementation, strengthening the position that exogenous sources of creatine increase its concentration also in the brain, where endogenous levels also increase. decrease with age, thus, with supplementation, it is possible to alleviate or delay these degenerative processes of neural diseases.

DISCUSSION

It was demonstrated, while reading the articles, that the effects of creatine supplementation in cases of Alzheimer's disease are promising, but still in their infancy. Creatine kinase (CK) is an enzyme found in several tissues of the human body, including the brain, where it is the main target of free radicals in the process of oxidative stress. This being the cause of neurodegeneration. It is in this factor that creatine intake is beneficial, as it protects CK against inactivation, providing neuroprotection. In addition, the supplement acts together with adenosine triphosphate (ATP) maintaining cellular energy homeostasis, preventing a decrease in energy metabolism and supporting the good state of the Central Nervous System (CNS) [26]. It is important to point out that the presence of creatine in the main organ of the CNS is not dependent on other systems or food, as production is endogenous. However, studies have shown that when this metabolic chain fails, supplementation alleviates the concentration deficit within the blood-brain barrier [19]. Another molecule that proved to be relevant when related to Alzheimer's disease and creatine consumption was phosphocreatine (PCr), which is the result of protein phosphorylation. The availability of PCr in the brain is small, but it is significant in bioenergetic merit. Physiologically, its levels differ between young and old, being related to a decrease in brain and physical activity, depression, schizophrenia and panic. That is, not necessarily with the age of the individual [26] - [19]. However, highlighting the progression of Alzheimer's disease, in the early stages, PCr activity decreases by up to 86% concomitantly with a 14% reduction in CK expression. Therefore, it is believed that the use of creatine supplements may contribute to the delay in the progression of neurodegenerative diseases, despite the increase in the PCr level being proportionally low, approximately 5 to 10% [21].

CONCLUSIONS

Concluding this integrative review and based on the studies presented, we know that Alzheimer's is a progressive degenerative disease of the Central Nervous System, characterized by deterioration of memory and multiple cognitive functions, such as orientation, language, learning and attention. Recent studies work with pharmacological alternatives, including the use of creatine supplementation. This substance is already widely used for sports

purposes and muscle performance, but it is evident that its role goes beyond the already known barriers and may have properties of therapeutic value with regard to neurodegeneration. However, the investigation of applicability is still at an early stage and the results are in the process of becoming evident. The current work contributes to the dissemination of the theme and to the stimulation of new research projects involving the theme.

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