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THE USE OF CREATINE BEYOND ERGOGENIC POTENTIAL: A NARRATIVE REVIEW

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INTRODUCTION

It is undeniable that nowadays the population has considerable interest in implementing a healthier lifestyle that involves a range of habits that can result in emotional, physical and mental balance, with the practice of a balanced diet, regular physical activity, adequate sleep and stress management. All this care is due to the aging population, which triggers greater concern about longevity. Although aging is a natural process, there are ways to promote it in a healthier way.

In this context, the use of dietary supplements is also included as a more frequent practice nowadays due to the search for a more active life, in addition to the fact that their use may be associated with nutritional deficiencies, increased nutritional demands or specific medical conditions. According to the Brazilian Association of the Food Industry for Special Purposes and Related Purposes (ABIAD, 2021), the consumption of dietary supplements by Brazilians increased by more than 10% in five years.

Among the supplements most consumed by those who practice physical activities, creatine stands out, due to its safety and effectiveness, which has already been scientifically proven to support its applicability. Basically, creatine is a nitrogenous amine with an ergogenic effect and potential applicability in clinical morbidities. The most used form in supplementation is creatine monohydrate, it is a safe and effective isoform and its difference lies in the formulation, as its composition involves creatine and a small portion of water, being tolerated more easily in the body (RAWSON ES, 2011).

There is robust evidence that supplementation has an ergogenic potential, promoting increased strength, improved resistance to muscle fatigue, bone density and enhanced post-exercise muscle recovery. Creatine is characterized by its ability to quickly provide energy to muscles in situations that require a more intense energy supply. In general terms, its physiological role is linked to the regeneration of ATP (adenosine triphosphate) in situations that demand intense energetic activity, involving both peripheral and central effects on the organism (KAZAK L, 2020; ANTONIO J et al., 2021).

Although creatine has its largest reserves in skeletal muscles, there is also a small amount present in brain tissue. Accordingly, brain creatine is associated with other benefits in addition to ergogenic potential, as it promotes better neuropsychological performance, preservation of brain function and improved cognitive processing.

Therefore, it can be concluded that its use is interesting in patients diagnosed with neurodegenerative diseases (SUMIEN N et al., 2018; BONILLA DA et al., 2021).

With the advancement of scientific research, many researchers felt encouraged to uncover other uses of creatine supplementation that go beyond its ergogenic potential. Therefore, it has been the subject of many studies to investigate its applicability in clinical morbidities involving neurological and cognitive dysfunctions, mitochondrial dysfunctions, metabolic conditions, creatine deficiency syndromes and muscular dystrophies (HARMON KK et al., 2021).

HISTORICAL CONTEXT OF CREATINE

Creatine is one of the most popular organic compounds in the field of clinical and sports nutrition. Historically, this natural compound was discovered in 1835 through the extraction of meat by Michel Chevreul, a French scientist and physiologist. He first named it "kreas", a term of Greek origin that means "flesh", inspiring many other scientists and chemists on the subject. A few years later, German

chemist Justus Von Liebig actually assured the true existence of this substance, and through research confirmed that the accumulation of creatine was greater in wild animals than in captivity, leading to the conclusion that muscular effort is linked to creatine deposit in the muscle. Given these findings, subsequent studies from the 20th century concluded that creatine is a substance associated with the process of muscle contraction and that its byproducts were also found in urine, in addition to unraveling the discovery of other isoforms and related enzymes, such as: free creatine, phosphorylated creatine and creatine kinase (DEMANT RHODES, 1999).

From this, in the last century, many researchers felt inspired to know and unveil a little more about the physiological action of creatine on human metabolism, due to the fact that it is not completely discarded in the urine. Therefore, a portion was stored in muscles and in other organs to a lesser extent, such as the brain and liver. Therefore, in 1950, synthetic creatine emerged through creation in the laboratory and since then has become one of the safest and most used supplements when seeking muscle optimization and better sports performance (BARROS et al., 2019).

In view of the above, the favorable role of creatine supplementation in terms of improving muscle mass and strength parameters is currently well established and consolidated. It is worth noting that the most commonly used form of supplementation is creatine monohydrate. Accordingly, there has been significant research interest regarding the potential that creatine supplementation can exert as a therapeutic target in pathological conditions of the human organism.

COMPOSITION AND METABOLISM OF CREATINE

Creatine is an organic compound that contains carbon, hydrogen and nitrogen in its composition, which comes from chemical reactions involving specific amino acids, such as: arginine, glycine and methionine. Although the body has the capacity to carry out its own synthesis of this compound, it is estimated that half of an individual's daily need comes from food, while the other part is replaced by its own production in the organs. Therefore, it must not be considered an essential nutrient, as its production occurs in the pancreas, liver, kidneys and also in brain cells. It is worth noting that whether creatine is consumed through supplementation or food, it is metabolized and absorbed together with the portion that is formed endogenously, therefore it can be concluded that a pool of creatine is generated in the body to be used in appropriate situations (KREIDER RB et al., 2017).

Creatine pools (reserves) are maintained through a biosynthetic pathway that encompasses two essential enzymes, glycine amidinotransferase (AGAT) and guanidinoacetate N-melthyltransferase (GAMT). In general terms, AGAT is responsible for catalyzing the amino acids glycine and arginine into guanidoacetate. The GAMT enzyme plays its role by causing guanidoacetate to be methylated into creatine in the liver. After the aforementioned process, creatine is distributed to tissues through SLC6A8 transporters, also called CRT1, CT1, CreaT or CRT (ELIDIE BÈARD et al., 2010).

Regarding the isoforms and physiological functioning of creatine, its action is directly aimed at energy metabolism through the immediate supply of energy in situations characterized by intense metabolic demand, exemplified by moments of "explosion" in some sports that require a greater amount

of energy. quickly in a short period of time. Basically, the mechanism is the transfer of the N-phosphoryl group from phosphorylcreatine (PCr) to adenosine diphosphate (ADP), thus forming a new molecule of adenosine triphosphate (ATP). The conversion of creatine into its analogue phosphocreatine is mediated by the enzyme creatine kinase (CK), which is expressed in tissues that have this profound energy demand (ROCHEL et al., 2021).

THE ROLE OF CREATINE IN NEURODEGENERATIVE DISEASES: IS THERE A RELATIONSHIP?

According to the Brazilian Society of Geriatrics and Gerontology (SBGG, 2011), neurodegenerative diseases correspond to a terminology that characterizes conditions associated with the progressive loss of neuronal cells in the nervous system. In final response, these are dysfunctions that result in gradual functional changes in the affected brain region and significant cognitive decline. According to epidemiological studies, it is a group of diseases that has been growing in recent years and represents a major public health concern, due to the triggering of economic and social consequences. According to the same scientific society, in Brazil, 55 thousand new cases of dementia are expected each year, the majority of which are diagnosed with Alzheimer's.

The nature of neurodegenerative diseases is also linked to aging, and has become one of the main causes of disability and lack of independence in the elderly population. Therefore, they are disorders that generate a decline and significant impairment in memory, behavior and the ability to carry out daily activities, as they lead to motor, sensory and also cognitive dysfunctions (CANDOW DG et al., 2021).

Of the hundreds of neurodegenerative disorders that are currently known, Alzheimer's disease, Parkinson's disease, Huntington's disease and Amyotrophic Lateral Sclerosis are the most dominant. Although there are many different diagnoses that encompass neurodegenerative diseases, studies by Petrovic et.al., (2020) demonstrated that there are similar conditions between them both in molecular and cellular factors, and therefore that they play a critical role in the evolution of the disease, specifically the poor aggregation of proteins, mitochondrial impairment, high production of reactive oxygen species and oxidative damage to biomolecules.

Analogous to this, recent studies associate the brain as an extremely active organ that demands a lot of energy and consumes around 20% of the energy available at rest, due to its activities in cellular processes and synaptic functioning.

Therefore, when comparing the weight of the brain, which is 2% of total body mass, with the need for energy (20%) used by the organ, the importance of maintaining a high level of energy renewal in brain tissue becomes evident (FORBES et al., 2022; TRIGO D et al., 2022).

Creatine is also found in the brain and is essential for maintaining energy levels in the nervous system. According to this statement, researcher Allen (2012) discusses in her studies that the pathophysiological trigger of neurodegenerative diseases leads to conditions that reduce brain creatine., with supplementation being a possible additional intervention in the treatment that could help combat oxidative damage and help minimize mitochondrial impairment, playing a role as a neuroprotective agent.

THE APPLICATION OF CREATINE SUPPLEMENTATION IN OTHER MORBIDITIES

Studies suggest that there is a current robust body of research in recent years that addresses the aspects and applicability of long-term creatine supplementation, as well as its precursor, guanidoacetic acid (GAA) as an attempt to increase brain creatine content and improve the brain bioenergetic mechanism (BRAISSANT et al., 2008; BARCELOS RP et al., 2016).

According to Brent Kious (2019), creatine monohydrate supplementation is interesting in many psychiatric disorders, with emphasis mainly on mental conditions of stress and depression, this is explained because such pathologies trigger changes in the brain pathway. The most discussed hypothesis is that creatine monohydrate is an antioxidant, neuromodulator and has a key potential for regulating energy metabolism, having a probable therapeutic value in pathologies involving metabolically compromised brains.

Creatine deficiency syndromes are cognitive deficits characterized as a group of inborn errors in creatine metabolism that affect its endogenous synthesis, mainly in the AGAT, GAMT and SLC6A8 transporters. They can be caused either by situations of acute stressful processes (stress, sleep deprivation, physical activities) or by chronic illnesses (exemplified by stroke, trauma, among others). Consequently, these are patients who will have greater difficulty in bioenergetic activity, mitochondrial abnormalities and dysfunctions, in addition to possible brain atrophy.

It is assumed that supplementation with creatine monohydrate for prolonged periods plays a fundamental role in these clinical cases, alleviating mental fatigue (MALHEIRO R et al., 2012; (BALESTRINO M et al., 2019).

Other research has evaluated the effects of creatine supplementation in individuals who are previously diagnosed with type 2 diabetes and results are promising in indicating that regular doses of creatine monohydrate are combined with an indication of better glucose tolerance. Based on other previous research, this hypothesis is also supported. (ALVES CR et al., 2012; KREIDER RB et al., 2021).

Regarding muscular dystrophies, Kylie Harmon (2021) reviews research that demonstrates that treatment can be considered for such conditions. In addition, in muscular dystrophies, free creatine stores are reduced. Therefore, creatine supplementation is of considerable importance in research, reporting benefits in the daily activities and functions of these patients, and also in the ability to articulate improvements in bone mineral density and lean mass content in children with muscular dystrophy.

Concisely, the function and performance of creatine in the human body will depend on which morbidity will be discussed. In all the diseases mentioned above there is some similarity, whether direct or indirect, with the production of reactive oxygen species (ROS), mitochondrial permeability, cell apoptosis or mitochondrial dysfunction. Studies by Gualano (2010) demonstrate that even though diseases have distinct pathophysiological roles, creatine supplementation is capable of promoting benefits in terms of antioxidant factors, neuromodulatory and neuroprotective aspects.

In view of the above, it becomes increasingly evident that creatine supplementation can be used as a therapeutic and prevention proposal for clinical dysfunctions or morbidities, demystifying the concept that its action is restricted only as an ergogenic agent, based on the creatine hypothesis monohydrate has applicability in acute or chronic conditions, focusing mainly on neurodegenerative diseases, in addition to addressing some

other morbidities that can benefit from supplementation, such as: mitochondrial dysfunctions, mental illnesses, muscular dystrophies and type 2 diabetes mellitus.

This review becomes relevant when discussing and analyzing the most current and consolidated research on the efficiency and application of creatine supplementation in various clinical conditions, both in its prevention and in association with drug treatment in the course of diseases, as one of the supplements most popular in the world, used as a strategy in both physiological and pathological conditions.

Therefore, the objective of the work is to investigate the role of creatine supplementation as a therapeutic strategy in different clinical morbidities, such as: neurodegenerative diseases, mental disorders, diabetes, mitochondrial dysfunctions and muscular dystrophies.

METHODOLOGY

This is a narrative review regarding the applicability of creatine in clinical morbidities. The methodological basis used for the construction of the work will be a narrative review, composed through selective bibliographical research of the literature, which will have as its database the National Library of Medicine (Pubmed), Scientific Electronic Library Online (SCIELO), Literature Latino-American and Caribbean Health Sciences (LILACS), Google Scholar and Periódicos Capes. Therefore, articles published between 2012 and 2022 will be included, covering data from scientific literature in English and Portuguese.

The key words used in the research will be: "creatine," "neurocognition," "supplementation," "mitochondrial disease," "applicability of creatine," "applicability of creatine," parkinson's disease", "mitochondrial cytopathies", "alzheimer's disease", "amyotrophic lateral sclerosis" and "creatine and aging". Different combinations of these terms will be used in order to promote greater reach and development of the research.

Studies outside the publication period between 2012 and 2022, articles due to duplication and those that do not address creatine as a therapeutic potential for pathological conditions, that is, that only evaluate the supplement as an ergogenic agent, will be excluded. Furthermore, no restrictions will be made regarding the age range and gender of the groups studied. Meta-analytic studies, experimental studies, systematic reviews and narrative reviews themselves will be included.

Regarding the article screening criteria, the possible presence of conflicts of interest in the selected research will be carefully evaluated, as it is a criterion capable of influencing the methodological choice, data analysis and interpretation of the results of a scientific study. Therefore, by choosing to select articles free of conflicts of interest, there is a greater guarantee that the results will be obtained impartially and based on solid scientific evidence.

In order to establish a prior organization among the selected articles, a first data collection will be assigned that includes the title of the article, year of publication, abstract and methodological characteristics, in accordance with all the exclusion criteria mentioned above. The guiding question that will be used throughout the construction of the project will be "What is the applicability of creatine in clinical conditions, in addition to its ergogenic potential in sports nutrition?".

RESULTS

The bibliographic survey was carried out from January to June 2023, in the different databases described previously, in which the following descriptors were used: "creatine," "neurocognition," "supplementation," "mitochondrial dysfunction", "applicability of creatine", "parkinson disease", "mitochondrial cytopathies", "alzheimer's disease", "amyotrophic lateral sclerosis" and "creatine and aging". A combination of controlled descriptors was used to ensure a comprehensive and accurate search. The initial search resulted in a broad set of potentially relevant studies.

In the first search, 182 scientific articles were found by reading the titles, abstracts and analysis of the year of publication, 115 of these were excluded, as they only addressed creatine supplementation as an ergogenic agent and were not focused on the therapeutic potential in clinical morbidities. In this screening phase, a data collection method was developed, including the following variables: year of publication, article title, general objective, methodological basis, study model and conclusion. Of the remaining 67 studies, their full texts were read and 51 were excluded for not meeting the pre-established inclusion criteria. It is worth noting that the searches were discarded due to duplication, and ultimately resulted in 16 articles chosen.

In this final screening, the high number of exclusions is explained due to the thorough analysis regarding the presence or absence of conflicts of interest between the authors and private institutions. This rigorous selection is essential in scientific research that will form a narrative review, with the aim of including the most robust and relevant articles in this analysis. This guarantees the validity of the results and a critical evaluation that involves the technical quality and reliability of previous studies.

DISCUSSION

MITOCHONDRIAL DYSFUNCTIONS

Mitochondrial dysfunction is a biological condition characterized when mitochondria, structures present in cells responsible for energy production, do not function correctly. Although a clear definition for this condition is not consolidated, basically the current literature refers to the scenario in which the organelle's ability to produce energy in the form of adenosine triphosphate (ATP) is reduced, so that any change in the normal function of the organelle can be treated as a "mitochondrial dysfunction". The cause of this variation in mitochondria may arise from a genetic change in mitochondrial DNA due to external factors, aging itself or exposure to harmful factors. Its cause may be secondary and correlated with the inheritance of pathological mitochondrial DNA. Furthermore, most DNA repair mechanisms decrease considerably with age, making it possible to relate an increase in these lesions to aging (SORRENTINO V et. al, 2018; JOHNSON J et.al, 2021).

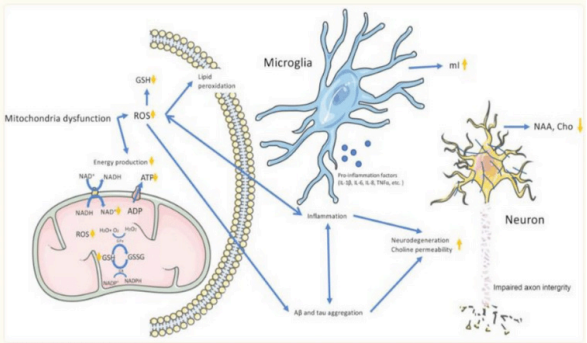

Figure 1: (KALISZEWSKA *et al*., 2021).

The figure above addresses the association of aging with the mitochondrial theory, so that mitochondria continue to be a key part in terms of disorders related to advancing age, increasing reactive oxygen species, mutations in DNA and in final response the triggering of

mitochondrial dysfunctions (KALISZEWSKA et al., 2021). According to research by Marshall RP (2022), the morbidities most related to the development of mitochondrial dysfunctions are: mitochondrial disease, acute myocardial infarction, chronic fatigue syndrome, long COVID, ischemia, hypoxia, stroke, neurodegenerative diseases, oxidative stress, as well as other non-communicable diseases.

There is evidence and indirect correlations between mitochondrial dysfunction and traumatic brain injuries, as well as the role that creatine supplementation may provide in this condition. In these injuries, cerebral oxidative respiration is affected by reduced blood flow (ischemia), so mitochondrial function is also impaired by increased intracellular calcium. This mechanism causes a cascade of reactions that are harmful to the body, as the mitochondria lose the ability to carry out oxidative respiration effectively and the production of ROS occurs. It is in this scenario that there is an energy issue in mild traumatic brain injuries, as an energy crisis and a demand for ATP are generated in an environment that has a low oxygen supply and ischemia. Given these conditions, creatine has an additional role in therapies for traumatic brain injuries (TBI), as it increases the availability of high-energy phosphate, and therefore increases mitochondrial efficiency and cell survival (AINSLEY DEAN PJ et al., 2017).

In a comprehensive analysis carried out by Marshall RP (2022), it was found that oral creatine monohydrate supplementation can be used as an additional therapy in the treatment of acute traumatic mitochondrial dysfunction. Physiologically, acute traumatic brain injury can cause an imbalance of ions such as calcium, potassium and sodium, and results in reduced mitochondrial functions. Furthermore, a state of ischemia is formed, in which there is a decrease in oxygen supply and interruption of the respiratory chain, in such a way that it impacts the mitochondria's ability to generate energy. This conclusion was based on randomized studies carried out in humans, in which patients with head trauma received a daily dose of 0.4 g/kg of creatine for 6 months, considered as a creatine monohydrate saturation protocol.

Both studies cited demonstrated that patients who received creatine supplementation had improvements in final clinical results, compared to the control group that did not receive supplementation. Such improvements in clinical parameters are attributed to the fact that creatine increases the ADP transport capacity for oxidative phosphorylation and the formation of phosphocreatine (Pcr), therefore compensating for short-term energy deficits. It is discussed that creatine demonstrates benefits by inhibiting the mitochondrial nucleotide translocator-creatine-adenine kinase (Mi-Cr-ANT) complex, since mitochondrial permeability is also associated with ischemia. It must be noted that in acute traumatic mitochondrial dysfunctions, reactive oxygen species are generated, causing oxidative stress and subsequently cellular damage. Therefore, creatine is beneficial in helping to combat free radicals given its antioxidant properties (MARSHALL RP et al., 2022; RABINOWITZ AR et al., 2014).

Already in a study with an experimental protocol in animals, it is worth mentioning the research by the author Saraiva AL (2012) who analyzed creatine supplementation in TBI in adult male Wistar rats. In general, it was concluded that creatine supplementation before TBI was able to reduce cortical damage and generated protection of mitochondrial function, as well as relevant protection from oxidative stress generated during the course of the pathology. It is necessary to mention that a reduction in markers of oxidative stress

caused by creatine supplementation was seen, but there were no improvements regarding susceptibility to seizures after acute traumatic brain injury due to supplementation. Despite its potential, experimental data on humans is still scarce, however the results of the few available studies are promising.

The premise of the correlation between mitochondrial dysfunctions and neurodegenerative diseases is based on the assumption that a deficiency in energy balance, as well as oxidative stress, leads to programmed cell death, and culminates in neuronal degeneration, especially in clinical conditions in which there is cognitive impairment of the individual. These pathologies are: Alzheimer's disease, amyotrophic lateral sclerosis, multiple lateral sclerosis, Huntington's disease and Parkinson's disease (SONG T et al., 2021; RIJPMA A et al., 2018).

NEURODEGENERATIVE DISEASES

In turn, the meta-analysis by Song T (2021) had the central idea of investigating and validating the model of oxidative stress and neuroinflammation, associated with mitochondrial dysfunction in patients with neurodegenerative morbidities. The article highlights research conducted in an experimental model with rodent animals with important findings, as it showed that with creatine supplementation there was a significant increase in phosphocreatine and inorganic phosphate in Alzheimer's disease, in which the author links mitochondrial dysfunction and oxidative stress which is found in pathology. Thus, the authors indicate that targeting abnormal bioenergetic processes associated with neurodegenerative diseases is a promising therapeutic intervention.

Accumulating evidence suggests that one of the therapeutic targets must be intervention in increasing brain energy metabolism, together with reducing free radicals and neural inflammation in neurodegenerative diseases. The studies conducted support energy deficit and mitochondrial dysfunction as aspects that play critical roles in the aging process and in the pathophysiology of diseases such as Alzheimer's and Parkinson's (BONKOWSKI and SINCLAIR DA, 2016; IMAI S and GUARENTE L, 2014; SONNTAG KC et al., 2014).

Among emerging therapeutic strategies, creatine monohydrate, a well-known dietary supplement, has attracted considerable interest for its additional role in mitigating the devastating effects of neurological conditions. Creatine is widely known for its association with physical and muscular performance and has been the subject of scientific studies that suggest a possible neuroprotective and modulating role in neurodegenerative diseases. The system that involves adenosine triphosphate, creatine kinase and phosphocreatine is recognized for maintaining bioenergetic balance in the central nervous system. Therefore, it is assumed that increasing brain creatine concentration is potentially beneficial for different clinical morbidities, with emphasis on neurodegenerative diseases in this section (AVEGERINOS KI et al., 2018).

The enzyme apparatus necessary for endogenous creatine synthesis is also found in the brain. This statement supports foundations regarding the possibility of using creatine in morbidities that affect cognition. According to Dolan (2019), there are twelve robust studies regarding the impact that creatine monohydrate supplementation has on brain creatine concentrations. Among the selected studies, nine showed a result in increasing brain creatine by around 5-10%. It is worth emphasizing that the increase is much smaller when compared to the increase in muscle, when there is supplementation in the same doses and criteria. This difference

can be explained by two factors: firstly, by the fact that brain tissue is more resistant to exogenous creatine, therefore a high dosage protocol is necessary over a longer period of analysis and the second factor is the limited permeability to creatine in the barrier. hematoencephalic disease (SOLIS MY et al., 2013; MEREGE-FILHO CAA et al., 2017).

Basically, brain creatine helps in situations where there is energy depletion, mitochondrial damage and oxidative stress, both conditions found in neurodegenerative diseases. A body of evidence summarizes that its results are more promising in cognition when individuals are subjected to stressors, such as: sleep deprivation and hypoxia (TURNER CE et al., 2015; FORBES et al., 2021). Particularly, the research carried out by Turner (2015) shows relevant findings as it represents one of the few experimental studies carried out on humans. Fifteen participants, aged between 21 and 55, were recruited to undergo a controlled state of hypoxia in order to investigate the potential positive impact of creatine monohydrate supplementation. This study adopted a randomized, double-blind model, in which participants received a daily supplement of 20g of creatine monohydrate or a placebo for a period of 5 weeks. The results revealed that the administration of creatine was able to alleviate cognitive impairments under hypoxic conditions, demonstrating a significant difference of 21% compared to the placebo group. It was found that creatine also promoted an increase in corticomotor excitability during oxygen deprivation. Therefore, it suggests a potential cognitive and neuromotor benefit of supplementation in hypoxic contexts.

A study conducted by Xiao (2014), randomized clinical trials were investigated that evaluated the effects of creatine compared to placebo in the treatment of Parkinson's disease, either as isolated supplementation or as a complementary treatment. Within this context, two clinical trials involving a total of 194 individuals with Parkinson's were analyzed. The supplementation protocol consisted of 20g of creatine daily for two years, followed by 2g daily for another six months and then 4g daily as a maintenance dose. The results showed no significant differences in relation to the improvement in the patients' motor function, and no positive aspect was seen in relation to the Parkinson's Disease Rating Scale (UPDRS) scores. The authors highlighted the need for more research dedicated to this topic, especially studies with a larger number of participants, as the sample used in the trials was considered small and the duration of the trials was relatively short, which could harm the evaluation of the results obtained.

Consolidating the hypothesis presented, another researcher Mo JJ (2017) conducted a meta-analysis by selecting five randomized clinical trials, encompassing a broad analysis of 1339 participants. Selection criteria covered the need for both trials to be randomized, controlled and double-blind, as well as patients needing to meet the clinical diagnostic criteria of the UK Parkinson's Disease Society Brain Bank, and finally, interventions must include creatine supplementation. Despite the considerable sample used in this study, no significant differences were identified between the control groups and patients who received placebo. In line with the previous study by Xiao (2014), this also did not demonstrate improvements in UPDRS scores with creatine supplementation.

Huntington's disease is a hereditary and progressive disease that affects the central nervous system and manifests itself through motor, cognitive and psychiatric disorders. Its evolution considerably compromises cognitive function and presents few therapeutic options. In order to investigate

whether creatine supplementation could contribute to delaying the decline in cognitive functions, Hersch (2017) conducted research whose methodology included characteristics of a multicenter, double-blind, randomized and placebo-controlled study. The study covered a group of 553 individuals, of which 275 received 40g of creatine monohydrate daily and 278 received a placebo over 48 months. Assessment of results was based on the rate of change in total functional capacity, variations in clinical scores, tolerability and quality of life. No significant differences were identified between men and women, and the rate of change in functional capacity was 0.82 points per year in the group that received creatine supplementation, and 0.70 points in participants in the placebo group (with an interval of nominal 95% confidence interval between -0.11 and 0.35), with the primary outcome measure being the rate of change in total functional capacity (TFC) between baseline and end of follow-up. However, no improvements were observed in other secondary parameters listed, leading to the conclusion that creatine supplementation did not prove to be a beneficial strategy in reducing symptoms in patients with early-stage Huntington's disease.

According to the World Health Organization (WHO, 2019), Alzheimer's disease has a prevalence of 60-70% of all cases of dementia and represents the most common cause of cognitive decline. As already mentioned in the section on mitochondrial dysfunctions, the main evidence regarding the potential of creatine supplementation in the therapeutic treatment of Alzheimer's is based on the concept of creatine exerting a neuroprotective effect and being related to correcting the parameters of mitochondrial dysfunctions and oxidative stress generated. (SMITH et al., 2014; ANDRES et al., 2019). In a study by Murray (2014), it was found that patients with Alzheimer's disease present hypometabolism in the regions that are most affected by the disease, as well as the expression and decreased activity of mitochondrial enzymes important for mitochondrial biogenesis. Therefore, it is suggested that creatine supplementation may have relevant therapeutic value in helping to combat mitochondrial dysfunctions.

In another study, researcher Smolarek (2020) conducted an analysis with elderly people of both sexes, whose physical and mental capabilities were preserved, and were subjected to a 5g creatine supplementation for 16 weeks, it is essential to emphasize that these elderly people were not diagnosed with Alzheimer's. During the study, a significant improvement in handgrip strength was observed, as well as an improvement in cognitive performance. Although the research was carried out in elderly people without cognitive decline, it is important to highlight that more research in humans must be carried out in order to analyze the therapeutic potential of supplementation in elderly people with larger samples, to evaluate cognitive function with larger samples and over a period of time. longer analysis period.

DIABETES MELLITUS

Diabetes mellitus is a chronic metabolic disease characterized by dysfunction in blood glucose regulation. Studies seek therapeutic strategies that help in the management of comorbidity, so creatine is indicated as a possible ally to treatment. Gualano (2011) carried out research to investigate whether creatine has a beneficial effect on glycemic control in type 2 diabetic patients undergoing physical training. The study was double-blind, randomized and placebo-controlled for 12 weeks. The sample included 25 individuals, half of whom received a dose of 5g of creatine daily and the other group received a placebo. As criteria, the curve of glucose, insulin,

C-peptide, insulin sensitivity index, physical capacity, lipid profile and expression and translocation of the GLUT-4 protein were analyzed.

This study addresses the premise that the potential of creatine to control diabetes is based on the increase in insulin secretion induced by supplementation, changes in osmoregulation, as well as the increase in glucose absorption induced by the translocation of glucose translocator 4 (GLUT-4). The study is correlated with physical activity and indicates that both interventions have a synergistic effect, when combined they promote greater benefits in glycemic control. The benefits with the group that supplemented with creatine were: reduction in glycated hemoblobin, area under the glucose concentration curve was significantly smaller, increased GLUT-4 translocation and decreased blood glucose (at times 0, 30 and 60 minutes). The parameters of C peptide, lipid profile and physical capacity were similar between the groups (GUALANO et al., 2011).

Supporting this finding, a very recent review by Marshall (2022) states that there is an intimate relationship between chronic non-communicable diseases and mitochondrial dysfunction. More specifically, it correlates that reduced levels of mitochondrial dysfunction were detected in diabetic patients with creatine supplementation. As a result, they report little mitochondrial dysfunction in diabetic patients when undergoing creatine supplementation. However, the author emphasizes the need for more recent experimental studies, both in animal models and in humans, to fully evaluate the therapeutic potential of creatine in this specific condition.

MENTAL DISORDERS

More than three decades ago, Agren and Niklasson (1984, 1988) began exploring the possible relationship between dysfunctional creatine metabolism and the pathophysiology of depression, identifying evidence supporting a connection between cerebral creatine metabolism and this psychiatric condition. More recent studies, such as the article by Allen (2012), suggest that reduced creatine metabolism may be associated with a less favorable clinical course for depression. In this study, positive correlations were observed between dopamine levels in cerebrospinal fluid, serotonin metabolites and creatine and creatinine levels in patients with depression.

These findings raise the possibility that changes in the creatine circuit may serve as a compensatory mechanism to combat the general metabolic deficits found in individuals with psychiatric illnesses, such that effective neurotransmission depends on adequate intracellular metabolism, which can be influenced by the creatine-phosphocreatine system. This complex interaction between creatine and depression offers interesting perspectives for the development of innovative therapeutic approaches, aiming to balance brain metabolism for a better clinical prognosis in affected patients (ALLEN PJ et al., 2012; LYOO IK et al., 2012).

In research conducted by Kondo (2011), the potential of creatine supplementation in female adolescents diagnosed with depression was evaluated. During the 8-week period, the teenagers received a daily supplement of 4g of creatine, and their results were compared with healthy teenagers who also underwent brain scans. The results revealed that the average Children's Rating Scale (CDRS-R) score dropped significantly from 69 to 30.6 after creatine supplementation. Although current research is limited, the authors suggest that the existence of mitochondrial dysfunction

and changes in bioenergetics may be related to depressive illness. Although inconclusive, the topic still arouses interest and requires further analysis, aiming to clarify the role of creatine in the treatment and management of this psychiatric condition.

Finally, the experimental study conducted by Toniolo (2018) addresses the topic with a larger sample in a double-blind study involving 35 patients diagnosed with bipolar disorder in depressive episodes, according to the criteria of the diagnostic and statistical system for classifying mental disorders. (DSM-IV). Participants were selected randomly, half of the group was assigned to receive placebo and the other half supplemented with creatine at a dose of 6g per day for 6 weeks. Outcomes were assessed using the Montgomery-Åsberg Depression Rating Scale (MADRS). No significant changes in the scale were observed between the two groups. However, an improvement was noted in patients who completed the study, with higher remission rates after 6 weeks. In the group that received creatine supplementation, eight patients (66.7%) achieved remission, compared to only two patients (18.2%) in the placebo group. These results, although promising, are not conclusive regarding the effectiveness of creatine supplementation in the treatment of bipolar depression, but suggest that this compound may play a relevant role as an additional treatment for morbidity.

More research is needed to more comprehensively understand the effects of creatine in bipolar disorder and to elucidate its true potential as a complementary therapy in this clinical context. Still, the findings represent an advance and encourage continued investigations into the use of creatine as a possible therapeutic tool in the management of bipolar depression.

MUSCULAR DYSTROPHIES

Muscular dystrophies constitute a diverse set of inherited degenerative genetic diseases that affect skeletal muscles. They are caused by approximately thirty known genes and proteins that result in different forms of muscular dystrophy. Such conditions share a common characteristic: the progressive and irreversible deterioration of muscle function, which leads to weakness, loss of muscle mass and impairment of mobility and quality of life in affected individuals. The essence of these dystrophies lies in the genetic alteration that affects the production of the dystrophin protein, leading to its deficiency or absence in the muscles. This results in fragility and progressive degeneration of muscle cells, consequently weakness and functional limitations. Unfortunately, there is currently no cure for these diseases, and available treatments focus on alleviating symptoms, improving quality of life and slowing the progression of the disease (MERCURI E et al., 2019; SHIEH PB, 2013).

In a study conducted by researcher Kley RA (2013), 14 randomized placebo-controlled clinical trials were analyzed, with a total sample of 364 participants. The hypothesis is that people with neuromuscular disorders have lower levels of creatine and phosphocreatine in skeletal muscles compared to healthy individuals, so the objective is to evaluate whether creatine supplementation could be an effective treatment. The results demonstrated a significant improvement in maximum voluntary contraction after supplementation, the average difference observed between the groups was 8.47%. The pooled analysis of four clinical trials with 115 participants revealed that a greater number of patients showed improvement in clinical status during creatine treatment compared to the placebo group. Such evidence suggests that short- and medium-term creatine

supplementation can increase muscle strength in patients with muscular dystrophy and influence the regulation of muscle protein metabolism. However, more studies are needed to consolidate these findings and further investigate the therapeutic potential of creatine for this neuromuscular condition.

FINAL CONSIDERATIONS

From the studies, the potential of creatine as a promising intervention in various clinical morbidities was observed. From critical analysis of a wide range of scientific evidence, it becomes clear that creatine has physiological and therapeutic properties that go beyond its traditional role in athletic performance. When investigating its impact on clinical problems such as neurodegenerative diseases, muscular dystrophies, psychiatric and metabolic disorders, it is evident that it plays an additional role in therapeutic bias, in a way that guarantees advantages with regard to cell defense, mitochondrial functioning, cognitive processes and neural protection.

The results show that supplementation can increase the availability of cellular energy, and thus appears to guarantee a substantial energy supply in situations characterized by energy deficiencies and mitochondrial dysfunction. The supplementation also has potential neural protection characteristics and antioxidant action, suggesting improvements in brain health and mental well-being. Regarding the impact on neurodegenerative diseases, although there is promising research, there are still divergent results in specific morbidities.

Finally, it is concluded that supplementation increases the concentration of creatine in the brain and ensures greater energy availability during unfavorable events and provides neuroprotection against traumatic brain injuries. However, it is essential to highlight that, although the results are encouraging, there are many gaps to be investigated. In this context, more robust studies are crucial, with larger samples so that an ideal protocol for supplementation in each condition mentioned can be defined.

When examining the therapeutic potential of creatine, it is important to recognize that certain limitations impact the interpretation of the results and the robustness of the study. One of the criticisms is the possibility of conflicts of interest between the authors and the supplement industry, making thorough investigation essential to guarantee the impartiality and integrity of the results.

Another point is the limited sample size, which compromises the representativeness and generalization of the results to a wider population. Due to the nature of the clinical diseases addressed, the heterogeneity of the patients studied is a crucial aspect. Age, stage of the disease, presence of comorbidities and genetic characteristics are points to be considered. Especially when investigating degenerative diseases, it is essential to note that the timeline and severity of declines in function vary between patients, and the presence of other adjunctive treatments makes it difficult to assess the specific contribution of creatine supplementation.

Another problem associated with the use of creatine in specific clinical morbidities is the lack of a standardized dose. Although research has investigated its beneficial potential in certain health conditions, the lack of clear guidelines regarding the exact amount to ingest raises concerns. Although research on the role of creatine in various diseases is promising, it is essential to recognize the limitations to guide future more comprehensive and well-designed studies. The applicability of these questions provides a deeper understanding of the topic and contributes to significant advances.

REFERENCES

1 Ainsley Dean PJ, Arikan G, Opitz B, Sterr A. Potential for use of creatine supplementation following mild traumatic brain injury. Concussion. 2017 Mar 21;2(2):CNC34. doi: 10.2217/cnc-2016-0016. PMID: 30202575; PMCID: PMC6094347.

2 Alves CR, Ferreira JC, de Siqueira-Filho MA, Carvalho CR, Lancha AH, Jr., Gualano B. Captação de glicose induzida por creatina no diabetes tipo 2: um papel para AMPK-alfa? *Amino*ácidos. 2012; 43 :1803–1807. doi: 10.1007/s00726-012-1246-6.

3 Allen PJ. Creatine metabolism and psychiatric disorders: Does creatine supplementation have therapeutic value? Neurosci Biobehav Rev. 2012 May;36(5):1442-62. doi: 10.1016/j.neubiorev.2012.03.005. Epub 2012 Mar 24. PMID: 22465051; PMCID: PMC3340488.

4 Andres RH, Ducray AD, Schlattner U, Wallimann T, Widmer HR, 2008. Funções e efeitos da creatina no sistema nervoso central. *C*érebro Res. Touro. 76, 329–343. 10.1016/j.brainresbull.2008.02.035. [PubMed] [CrossRef] [Google Acadêmico

5 Antonio J, Candow DG, Forbes SC, Gualano B, Jagim AR, Kreider RB, Rawson ES, Smith-Ryan AE, VanDusseldorp TA, Willoughby DS, Ziegenfuss TN. Common questions and misconceptions about creatine supplementation: what does the scientific evidence really show? J Int Soc Sports Nutr. 2021 Feb 8;18(1):13. doi: 10.1186/s12970-021-00412-w. PMID: 33557850; PMCID: PMC7871530.

6 Avgerinos KI, Spyrou N, Bougioukas KI, Kapogiannis D. Effects of creatine supplementation on cognitive function of healthy individuals: A systematic review of randomized controlled trials. Exp Gerontol. 2018 Jul 15;108:166-173. doi: 10.1016/j.exger.2018.04.013. Epub 2018 Apr 25. PMID: 29704637; PMCID: PMC6093191.

7 Balestrino M, Adriano E. Beyond sports: Efficacy and safety of creatine supplementation in pathological or paraphysiological conditions of brain and muscle. Med Res Rev. 2019 Nov;39(6):2427-2459. doi: 10.1002/med.21590. Epub 2019 Apr 23. PMID: 31012130.

8 Barcelos RP, Stefanello ST, Mauriz JL, Gonzalez-Gallego J, Soares FA. Creatine and the Liver: Metabolism and Possible Interactions. Mini Rev Med Chem. 2016;16(1):12-8. doi: 10.2174/1389557515666150722102613. PMID: 26202197.

9 BARROS, ANA PAULA PEREIRA. Suplementação de creatina para o treinamento de força. Revista Uningá, PARANÁ, v. V.56, n. N.1, p. 91-97, 25 abr. 2019. Disponível em: https://repositorio.unesp.br/bitstream/handle/11449/136606/000859831.pdf?sequenc. Acesso em: 25 abr. 2023.

10 Bonilla DA, Kreider RB, Stout JR, Forero DA, Kerksick CM, Roberts MD, Rawson ES. Metabolic Basis of Creatine in Health and Disease: A Bioinformatics-Assisted Review. Nutrients. 2021 Apr 9;13(4):1238. doi: 10.3390/nu13041238. PMID: 33918657; PMCID: PMC8070484

11 Bonkowski MS, Sinclair DA, 2016. Retardar o envelhecimento por design: o aumento de NAD + e compostos de ativação de sirtuína. *Nat. Rev. Mol. Cell Biol*. 17, 679-690. 10.1038/nrm.2016.93. [Artigo gratuito do PMC] [PubMed] [CrossRef] [Google Scholar]

12 Braissant O, Henry H. AGAT, GAMT and SLC6A8 distribution in the central nervous system, in relation to creatine deficiency syndromes: a review. J Inherit Metab Dis. 2008 Apr;31(2):230-9. doi: 10.1007/s10545-008-0826-9. Epub 2008 Apr 4. PMID: 18392746.

Brand MD, Nicholls DG. Assessing mitochondrial dysfunction in cells. Biochem J. 2011 Apr 15;435(2):297-312. doi: 10.1042/BJ20110162. Erratum in: Biochem J. 2011 Aug 1;437(3):575. PMID: 21726199; PMCID: PMC3076726.

13 Candow DG, Forbes SC, Kirk B, Duque G. Current Evidence and Possible Future Applications of Creatine Supplementation for Older Adults. Nutrients. 2021 Feb 26;13(3):745. doi: 10.3390/nu13030745. PMID: 33652673; PMCID: PMC7996960.

14 Correa, A. B. F., Viana, V. M., Laranjeira, G., Gonçalves, E. de V., Rocha, G. F., Madeira, K., & Luciano, T. F. (2022). Conhecimento sobre a suplementação de creatina em praticantes de musculação. *RBNE - Revista Brasileira De Nutrição Esportiva*, *16*(96), 34-45.

15 DEMANT, T.W.; RHODES, E.C. Effects of creatine supplementation on exercise performance. Sports Med, V. 28, p. 9-60, julho, 1999.

Dolan E, Gualano B, Rawson ES. Beyond muscle: the effects of creatine supplementation on brain creatine, cognitive processing, and traumatic brain injury. Eur J Sport Sci. 2019 Feb;19(1):1-14. doi: 10.1080/17461391.2018.1500644. Epub 2018 Aug 7. PMID: 30086660.

16 Elidie Béard, Oliver Braissant.Synthesis and transport of creatine in the CNS: importance for cerebral functions. Journal of Neurochemistry,2010 October; 297-313. doi: 10.1111/j.1471-4159.2010.06935.x.

17 Forbes SC, Cordingley DM, Cornish SM, Gualano B, Roschel H, Ostojic SM, Rawson ES, Roy BD, Prokopidis K, Giannos P, Candow DG. Effects of Creatine Supplementation on Brain Function and Health. Nutrients. 2022 Feb 22;14(5):921. doi: 10.3390/nu14050921. PMID: 35267907; PMCID: PMC8912287.

Forbes S., Candow D., Ferreira L., Souza-Junior T. Efeitos da suplementação de creatina nas propriedades dos músculos, ossos e função cerebral em adultos mais velhos: uma revisão narrativa. *J. Dieta. Supl.* 2021:1–18. doi: 10.1080/19390211.2021.1877232. [PubMed] [CrossRef] [Google Acadêmico]

18 Gualano B., V DESP, Roschel H., Artioli GG, Neves M., Jr., De Sa Pinto AL, Da Silva ME, Cunha MR, Otaduy MC, Leite Cda C., et al. Creatina no diabetes tipo 2: um estudo randomizado, duplo-cego, controlado por placebo. *Med. ciência Exercício Esportivo.* 2011; 43 :770–778. doi: 10.1249/MSS.0b013e3181fcee7d.

19 Harmon KK, Stout JR, Fukuda DH, Pabian PS, Rawson ES, Stock MS. The Application of Creatine Supplementation in Medical Rehabilitation. Nutrients. 2021 May 27;13(6):1825. doi: 10.3390/nu13061825. PMID: 34071875; PMCID: PMC8230227.

20 Hersch SM, Schifitto G, Oakes D, Bredlau AL, Meyers CM, Nahin R, Rosas HD; Huntington Study Group CREST-E Investigators and Coordinators. The CREST-E study of creatine for Huntington disease: A randomized controlled trial. Neurology. 2017 Aug 8;89(6):594-601. doi: 10.1212/WNL.0000000000004209. Epub 2017 Jul 12. PMID: 28701493; PMCID: PMC5562960

21 llen PJ. Creatine metabolism and psychiatric disorders: Does creatine supplementation have therapeutic value? Neurosci Biobehav Rev. 2012 May;36(5):1442-62. doi: 10.1016/j.neubiorev.2012.03.005. Epub 2012 Mar 24. PMID: 22465051; PMCID: PMC3340488

Imai S, Guarente L, 2014. NAD + e sirtuínas no envelhecimento e na doença. *Trends Cell Biol*. 24, 464-471. 10.1016/j.tcb.2014.04.002. [Artigo gratuito do PMC] [PubMed] [CrossRef] [Google Scholar]

22 Johnson J, Mercado-Ayon E, Mercado-Ayon Y, Dong YN, Halawani S, Ngaba L, Lynch DR. Mitochondrial dysfunction in the development and progression of neurodegenerative diseases. Arch Biochem Biophys. 2021 May 15;702:108698. doi: 10.1016/j.abb.2020.108698. Epub 2020 Nov 28. PMID: 33259796

23 Kaliszewska A, Allison J, Martini M, Arias N. Improving Age-Related Cognitive Decline through Dietary Interventions Targeting Mitochondrial Dysfunction. Int J Mol Sci. 2021 Mar 30;22(7):3574. doi: 10.3390/ijms22073574. PMID: 33808221; PMCID: PMC8036520.

24 Kazak L, Cohen P. Creatine metabolism: energy homeostasis, immunity and cancer biology. Nat Rev Endocrinol. 2020 Aug;16(8):421-436. doi: 10.1038/s41574-020-0365-5. Epub 2020 Jun 3. PMID: 32493980.

25 Kious BM, Kondo DG, Renshaw PF. Creatine for the Treatment of Depression. Biomolecules. 2019 Aug 23;9(9):406. doi: 10.3390/biom9090406. PMID: 31450809; PMCID: PMC6769464.

26 Kley RA, Tarnopolsky MA, Vorgerd M. Creatine for treating muscle disorders. Cochrane Database Syst Rev. 2013 Jun 5;2013(6):CD004760. doi: 10.1002/14651858.CD004760.pub4. PMID: 23740606; PMCID: PMC6492334

27 Kreider RB, Kalman DS, Antonio J, Ziegenfuss TN, Wildman R, Collins R, Candow DG, Kleiner SM, Almada AL, Lopez HL. International Society of Sports Nutrition position stand: safety and efficacy of creatine supplementation in exercise, sport, and medicine. J Int Soc Sports Nutr. 2017 Jun 13;14:18. doi: 10.1186/s12970-017-0173-z. PMID: 28615996; PMCID: PMC5469049.

28 Kreider RB, Stout JR. Creatine in Health and Disease. Nutrients. 2021 Jan 29;13(2):447. doi: 10.3390/nu13020447. PMID: 33572884; PMCID: PMC7910963.

29 Leia CY, Calnan RJ Doença mitocondrial: além da etiologia desconhecida. *J. Pediatr. Enfermeiras.* 2000; 15 :232–241. doi: 210.1053/jpdn.2000.8042. [PubMed] [CrossRef] [Google Scholar] [Lista de referências

30 LOPES, LC. Doença de alzheimer: prevenção e tratamento. Sociedade Brasileira de Geriatria e Gerontologia, [*S. l.*], p. 2-18, 31 jan. 2011.

31 Lyoo IK, Yoon S., Kim TS, Hwang J., Kim JE, Won W., Bae S., Renshaw PF Um estudo randomizado, duplo-cego, controlado por placebo, de aumento oral de monohidrato de creatina para resposta aprimorada a um inibidor seletivo de recaptação de serotonina em mulheres com transtorno depressivo maior. *Sou. J. Psiquiatria.* 2012; 169 :937–945. doi: 10.1176/appi.ajp.2012.12010009. [Artigo gratuito do PMC] [PubMed] [CrossRef] [Google Scholar]

32 Malheiro R, Diogo L, Garcia P, Fineza I, Oliveira G. Síndromes de deficiência cerebral de creatina [Cerebral creatine deficiency syndromes]. Acta Med Port. 2012 Nov-Dec;25(6):389-98. Portuguese. Epub 2013 Jan 28. PMID: 23534590.

33 Marshall RP, Droste JN, Giessing J, Kreider RB. Role of Creatine Supplementation in Conditions Involving Mitochondrial Dysfunction: A Narrative Review. Nutrients. 2022 Jan 26;14(3):529. doi: 10.3390/nu14030529. PMID: 35276888; PMCID: PMC8838971.

34 Mercuri E, Bönnemann CG, Muntoni F. Muscular dystrophies. Lancet. 2019 Nov 30;394(10213):2025-2038. doi: 10.1016/S0140-6736(19)32910-1. PMID: 31789220.

35 Merege-Filho CAA, Otaduy MCG, De Sá-Pinto AL, De Oliveira MO, Gonçalves LDS, Hayashi APT, Roschel H., Pereira RMR, Silva CA, Brucki SMD, et al. O conteúdo de creatina cerebral depende da creatina exógena na juventude saudável? Um estudo de prova de princípio. *Appl. Physiol. nutr. Metab.* 2017; 42 :128–134. doi: 10.1139/apnm-2016-0406. [PubMed] [CrossRef] [Google Acadêmico]

36 Mo JJ, Liu LY, Peng WB, Rao J, Liu Z, Cui LL. The effectiveness of creatine treatment for Parkinson's disease: an updated meta-analysis of randomized controlled trials. BMC Neurol. 2017 Jun 2;17(1):105. doi: 10.1186/s12883-017-0885-3. PMID: 28577542; PMCID: PMC5457735.

37 Murray J, Tsui WH, Li Y, McHugh P, Williams S, Cummings M, Pirraglia E, Solnes L, Osorio R, Glodzik L, Vallabhajosula S, Drzezga A, Minoshima S, de Leon MJ, Mosconi L. FDG and Amyloid PET in Cognitively Normal Individuals at Risk for Late-Onset Alzheimer's Disease. Adv J Mol Imaging. 2014 Apr;4(2):15-26. doi: 10.4236/ami.2014.42003. PMID: 25530915; PMCID: PMC4270202.

38 Niklasson F, Agren H. Metabolismo energético do cérebro e permeabilidade da barreira hematoencefálica em pacientes depressivos: análises de creatina, creatinina, urato e albumina no líquido cefalorraquidiano e no sangue. *Psiquiatria Biol.* 1984; 19 :1183–1206. [PubMed] [Google Acadêmico

39 Oliveira, A. S. (2019). Transição demográfica, transição epidemiológica e envelhecimento populacional no Brasil. Hygeia-Revista Brasileira de Geografia Médica e da Saúde, 15(32), 69-79.

40 Petrovic S, Arsic A, Ristic-Medic D, Cvetkovic Z, Vucic V. Lipid Peroxidation and Antioxidant Supplementation in Neurodegenerative Diseases: A Review of Human Studies. Antioxidants (Basel). 2020 Nov 13;9(11):1128. doi: 10.3390/antiox9111128. PMID: 33202952; PMCID: PMC7696060.

41 Rawson ES, Venezia AC. Use of creatine in the elderly and evidence for effects on cognitive function in young and old. Amino Acids. 2011 May;40(5):1349-62. doi: 10.1007/s00726-011-0855-9. Epub 2011 Mar 11. PMID: 21394604.

Rijpma A, van der Graaf M, Meulenbroek O, Olde Rikkert MGM, Heerschap A. Altered brain high-energy phosphate metabolism in mild Alzheimer's disease: A 3-dimensional 31P MR spectroscopic imaging study. Neuroimage Clin. 2018 Feb 28;18:254-261. doi: 10.1016/j.nicl.2018.01.031. PMID: 29876246; PMCID: PMC5987799.

42 Roschel H, Gualano B, Ostojic SM, Rawson ES. Creatine Supplementation and Brain Health. Nutrients. 2021 Feb 10;13(2):586. doi: 10.3390/nu13020586. PMID: 33578876; PMCID: PMC7916590.

43 Saraiva AL, Ferreira AP, Silva LF, Hoffmann MS, Dutra FD, Furian AF, Oliveira MS, Fighera MR, Royes LF. Creatine reduces oxidative stress markers but does not protect against seizure susceptibility after severe traumatic brain injury. Brain Res Bull. 2012 Feb 10;87(2-3):180-6. doi: 10.1016/j.brainresbull.2011.10.010. Epub 2011 Oct 25. PMID: 22051612.

44 Shieh PB. Muscular dystrophies and other genetic myopathies. Neurol Clin. 2013 Nov;31(4):1009-29. doi: 10.1016/j.ncl.2013.04.004. PMID: 24176421.

Smith RN, Agharkar AS, Gonzales EB, 2014. Uma revisão da suplementação de creatina em doenças relacionadas à idade: mais do que um suplemento para atletas. *F1000Res*. 3, 222. 10.12688/f1000research.5218.1. [Artigo gratuito do PMC] [PubMed] [CrossRef] [Google Scholar]

45 Smolarek AC, McAnulty SR, Ferreira LH, Cordeiro GR, Alessi A., Rebesco DB, Honorato IC, Laat EF, Mascarenhas LP, Souza-Junior TP Effect of 16 Weeks of Strength Training and Creatine Supplementation on Strength and Cognition in Older Adults: A Pilot Study. *J. Exerc. Physiol. On-line.* 2020; 23 :88–94.

46 Solis MY, Painelli VDS, Artioli GG, Roschel H., Otaduy MC, Gualano B. Depleção de creatina cerebral em vegetarianos? Um estudo transversal de espectroscopia de ressonância magnética 1H (1H-MRS). *Br. J. Nutr.* 2013; 111 :1272–1274. doi: 10.1017/S0007114513003802. [PubMed] [CrossRef] [Google Acadêmico]

47 Song T, Song X, Zhu C, Patrick R, Skurla M, Santangelo I, Green M, Harper D, Ren B, Forester BP, Öngür D, Du F. Mitochondrial dysfunction, oxidative stress, neuroinflammation, and metabolic alterations in the progression of Alzheimer's disease: A meta-analysis of in vivo magnetic resonance spectroscopy studies. Ageing Res Rev. 2021 Dec;72:101503. doi: 10.1016/j.arr.2021.101503. Epub 2021 Oct 29. PMID: 34751136; PMCID: PMC8662951.

48 Sonntag KC, Ryu WI, Amirault KM, Healy RA, Siegel AJ, McPhie DL, Forester B, Cohen BM, 2017. A doença de Alzheimer de início tardio está associada a alterações inerentes nos perfis bioenergéticos. *ciência Rep*. 7, 14038. 10.1038/s41598-017-14420-x. [Artigo gratuito do PMC] [PubMed] [CrossRef] [Google Scholar]

49 Sorrentino V, Menzies KJ, Auwerx J. Repairing Mitochondrial Dysfunction in Disease. Annu Rev Pharmacol Toxicol. 2018 Jan 6;58:353-389. doi: 10.1146/annurev-pharmtox-010716-104908. Epub 2017 Sep 27. PMID: 28961065.

50 Sumien N, Shetty RA, Gonzales EB. Creatine, Creatine Kinase, and Aging. Subcell Biochem. 2018;90:145-168. doi: 10.1007/978-981-13-2835-0_6. PMID: 30779009.

51 Toniolo RA, Silva M, Fernandes FBF, Amaral JAMS, Dias RDS, Lafer B. A randomized, double-blind, placebo-controlled, proof-of-concept trial of creatine monohydrate as adjunctive treatment for bipolar depression. J Neural Transm (Vienna). 2018 Feb;125(2):247-257. doi: 10.1007/s00702-017-1817-5. Epub 2017 Nov 24. PMID: 29177955; PMCID: PMC5775367

52 Trigo D, Avelar C, Fernandes M, Sá J, da Cruz E Silva O. Mitochondria, energy, and metabolism in neuronal health and disease. FEBS Lett. 2022 May;. doi: 10.1002/1873-3468.14298. 3 fev. 2022. PMID: 35088449.

53 Turner CE, Byblow WD, Gant N. A suplementação de creatina aumenta a excitabilidade corticomotora e o desempenho cognitivo durante a privação de oxigênio. *J. Neurosci.* 2015; 35 :1773-1780. doi: 10.1523/JNEUROSCI.3113-14.2015. [Artigo gratuito do PMC] [PubMed] [CrossRef] [Google Scholar]