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Beta-amyloid plaque deposits and increased tau protein in the early diagnosis of alzheimer's disease: the importance of physical activity in the prevention and evolution of the patient

Abstract

In recent years, it has become clear that the β-amyloid (Aβ) component of senile plaques may be the key molecule in the pathology of Alzheimer's disease (AD). However, the origin and site of Aβ's neurotoxic action are still the subject of controversy. The precursor of the β-amyloid peptide is the β-amyloid precursor protein, which is predominantly neuronal. The hypothesis is that intraneuronal dysregulation of Amyloid Precursor Protein (APP) leads to the accumulation of Aβ peptides in intracellular compartments. This accumulation impairs the trafficking of APP, which initiates a cascade of pathological changes and causes the degeneration of pyramidal neurons. The increased secretion of Aβ as a function of stressed neurons and degenerated neuron remnants provides seeds for extracellular Aβ aggregates, which induce secondary degenerative events involving neighboring cells such as neurons, astroglia and macrophages/microglia. The benefits of physical exercise to reduce low-grade inflammation and improve cognitive function have become a growing field of interest. Epidemiological research has shown that a sedentary lifestyle intensifies the processes of disability and dependence, and also increases the incidence of chronic diseases. Physical exercise has been inversely associated with high levels of different inflammatory markers. It plays a neurotrophic role, capable of promoting a reduction in the accumulation of β-amyloid peptide and the hyperphosphorylation of tau protein, being an important alternative pathway for reducing the degenerative process, which does not result in the release of pro-inflammatory factors, as well as helping to reduce the levels of pro-inflammatory cytokines and improve peripheral concentrations.

Keywords: alzheimer's disease, inflammation, inflammatory biomarkers, physical exercise, aging

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Juliana F B Paschoal,[1] Délio T M Malaquias,[1] Isadora O Soler,[1] Victória B S Miguel,[1] Júlio E Calheiros,[1] Giovana R Victorello,[1] Isabeli G de Oliveira,[1] Thalita P M Alineri,[1] Jenyffer V C Villca,[1] João Paulo P Santos,[1] Kevin N Silva,[1] Mariana C de Oliveira,[1] Maria Fernanda N V Da Silva,[1] Hamilton Roberto M de O Carriço,[2] Aldaiana Scarsi,[3] Giovana C Bitolo,[4] Christopher A P Lima,[4] Amanda L B Cordeiro,[5] Natália L Medici,[6] Rafaela D G Reis,[1] Ana Clara P R de Souza,[1] Gabriella C A S R Farias,[1] Caio V de Sa Bertozzi,[1] Livia S Bomfim,[1] Luan N Lázaro,[1] Alessandra S de Freitas,[1] Júlia da S Toledo,[1] Isabela F Krebs,[1] Bruna D Araujo,[1] Jheniffer R Cação,[1] Lucas V de Melo,[1] Rafael N Rebucci,[1] Amanda D de Macedo,[1] Maria Paula M Nogueira,[1] Breno B Gallo,[1] Leonardo T da Silva,[1] Daniela S BL Dos Santos,[1] Adriana F V Delgado,[1] Ana Carolina P Bergamin,[1] Elysa F Camargo, I Vitor H de Souza,[1] Thiago A Rochetti Bezerra[1–7]

[1]Medical student, University of Ribeirão Preto. Guarujá, São Paulo, Brazil
[2]Medical student, University of the South of Santa Catarina. Tubarão, Santa Catarina. Brazil
[3]Medical student, Universidad Central del Paraguay, Paraguay
[4]Medical student, Nove de Julho University. São Bernardo do Campo, Brazil
[5]Medical student, Potiguar University, Natal, Rio Grande do Norte, Brazil
[6]Medical student, University of the West of São Paulo, Guarujá, Brazil
[7]PhD in Medical Sciences, Ribeirão Preto Medical School. University of São Paulo. Ribeirão Preto, Brazil

Correspondence: Thiago A Rochetti Bezerra, Medical student, University of Ribeirão Preto. Guarujá, São Paulo, Brazil, Email rochetti.se@gmail.com

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Introduction

The demographic transition, which has resulted in an increase in longevity, has brought with it significant changes in the epidemiological profile. Chronic and degenerative diseases have become more prominent than infectious and contagious conditions. One of the consequences of this ageing population is the greater prevalence of chronic conditions, especially dementias.[1]

Data from the Brazilian Institute of Geography and Statistics (IBGE) estimates that, by 2050, there will be around 64 million elderly people in Brazil (IBGE, 2023). Furthermore, it is estimated that in the same year, more than 25% of the world's population will be elderly.[2] Therefore, this data is extremely important for researchers because, as they realize the annual increase in the elderly population, understanding the causes and treatments for Alzheimer's Disease (AD) becomes an urgent necessity.

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According to data from the World Health Organization (2023), mental disorders account for around 15% of the global burden of disease, with AD being the most prevalent form of dementia in the elderly. It is estimated that there are around 35.6 million people with dementia in the world, and this figure could reach 115.4 million by 2050.[3]

It is believed that cases of dementia are directly related to advancing age, and according to Herrera Júnior et al.,[4] approximately 55% of dementia diagnoses in a psychiatric outpatient clinic were attributed to AD. In addition, physical inactivity is another factor that influences the development of AD and can be modified.[5]

Based on these statistics, evidence suggests that the prevalence of AD doubles every five years from the age of 65 to 90.[6] In recent years, several studies have been conducted on AD and its possible causes, as well as ways of preventing it using inflammatory biomarkers. AD is a neurodegenerative condition characterized by multiple cognitive deficits, of continuous and irreversible progression, whose etiology remains unknown, and is manifested mainly by complaints related to memory.

The main histopathological changes in this process result from the accumulation of beta-amyloid protein, forming senile plaques, and neurofibrillary tangles, resulting from the hyperphosphorylation of thetau protein, which occur predominantly in the temporal lobe regions.[6] During the ageing process, some metabolic alterations often result in changes in the action of the immune system, characterizing a picture of low-grade systemic inflammation. Associated with this condition, the degenerative process can intensify. "The neuroinflammation that occurs in response to the deposition of beta-amyloid peptide (βAP) in AD appears to be one of the main components of the disease's pathology".[7] However, physical activity can be used as a non-pharmacological approach to preventing AD and has shown great influence in controlling the disease. The release of some hormones has an immunomodulatory action, inhibiting the action of cytokines that can interfere with the degenerative process.[8]

In addition, regular physical exercise can reduce the risk of chronic and metabolic diseases. This is due to the anti-inflammatory effect that exercise produces due to the reduction in visceral adipose tissue, which consequently generates a decrease in the release of adipokines, and induces the body into an anti-inflammatory environment.[9] Therefore, this study is a literature review and aims to analyze the inflammatory mechanisms that are precursors of the disease, as well as highlighting the relevance of physical exercise in its prevention. The study was based on a review of previously published works, with the aim of describing the evidence found in the literature.

Methodology

This research is a literature review, which consisted of a search and analysis of articles, with the aim of reviewing the inflammatory mechanisms that are precursors of Alzheimer's disease and precursors of Alzheimer's disease and relate the effects of physical activity in its prevention, through a bibliographic survey in the databases of websites and indexed journals of the CAPES Journals Portal from 2004 to 2024, using as descriptors: Alzheimer's disease, Alzheimer's disease, Inflammatory biomarkers, Physical Exercise and Aging.

The selection of material was based on the objective proposed by the study, with the inclusion criteria being articles that were related and relevant to the topic. We selected longitudinal, randomized studies; samples made up of individuals with a probable diagnosis of AD and cognitively preserved individuals in which physical activity was used as a variable. Articles were excluded if the title was not related to the proposed topic and, when necessary, the abstract and methods of the study.

Results and discussion

It is unknown what causes Alzheimer's disease, but part of it comes from genetic factors: Around 5 to 15% of cases affect people with a family history. Several specific genetic abnormalities may be involved. Some of these abnormalities can only be inherited when one of the parents has the abnormal gene. In other words, the abnormal gene is dominant. An affected parent has a 50% chance of passing on the abnormal gene to each child. Around half of these children develop Alzheimer's disease before the age of 65.[10]

According to Porsteinsson et al.,[11] in most other cases, a single gene is not dominant. Instead, other genes affect the risk of developing Alzheimer's disease. One genetic abnormality affects apolipoprotein E (apo E) - the part of the protein in some lipoproteins that transports cholesterol through the bloodstream.

There are three types of apo E:

Epsilon 4: People with the epsilon-4 type develop Alzheimer's disease more commonly and earlier than others.

Epsilon 2: In contrast, people with the epsilon-2 type seem to be protected against Alzheimer's disease.

Epsilon 3: People with the epsilon-3 type are neither protected nor more likely to develop the disease.

However, genetic testing for apo E type cannot determine whether a specific person will develop Alzheimer's disease. Therefore, this test is not routinely recommended.[11] The studies by Zhang et al.[12] cite that Alzheimer's disease causes the following abnormalities in the development of brain tissue:

- Beta-amyloid deposits: Accumulation of beta-amyloid (an abnormal, insoluble protein) which builds up because the cells cannot process and remove it.

- Neuritic (senile) plaques: Clusters of dead nerve cells around a nucleus of beta-amyloid.

Around a beta-amyloid core:

- Neurofibrillary braids: Braided strands of insoluble proteins in the nerve cell

- Increased levels of tau: An abnormal protein component of neurofibrillary braids and beta-amyloid.

These abnormalities develop to some degree in everyone as they get older, but they are much more numerous in people with Alzheimer's disease. Doctors are not sure whether abnormalities in brain tissue cause Alzheimer's disease or result from some other problem that causes both dementia and abnormalities in brain tissue to occur.[13]

Researchers Vitek, Decourt & Sabbagh[14] found that the abnormal proteins in Alzheimer's disease (beta-amyloid and tau) resemble the abnormal proteins in diseases caused by prions. In other words, they misfold and cause other proteins to misfold, leading to the progression of the disease. Inflammation can also contribute to the development of Alzheimer's disease. Inflammation has been observed in the brains of people with Alzheimer's disease.

Beta-amyloid deposits

The amyloid hypothesis (Figure 1), postulates that the progressive accumulation of beta-amyloid in the brain triggers a complex cascade

of events that end in neuronal cell death, loss of neuronal synapses and progressive neurotransmitter deficits; all these effects contribute to the clinical symptoms of dementia.[14]

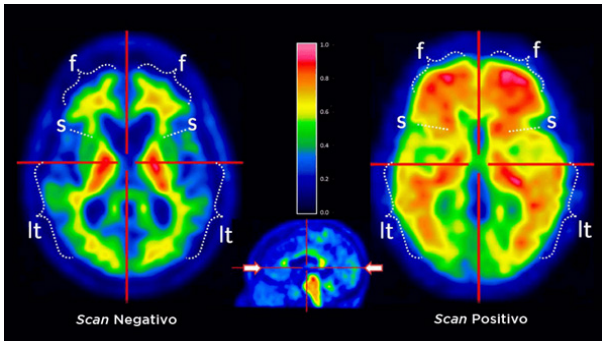

Figure 1 PET scan with a special marker to identify amyloid plaques in the brains of patients with Alzheimer's disease.

Source: Researchgate.net/figure/Axial-images-of-an-amyloid-PET-CT.

Plaques are formed when pieces of the protein called beta-amyloid clump together. Beta-amyloids come from a larger protein found in the fatty membrane that surrounds nerve cells. Beta-amyloid is chemically "sticky" and gradually sticks together to form plaques.[15] Perhaps the most harmful forms of beta-amyloid are the clusters of small pieces rather than the plaques themselves. The small clusters can block signaling between cells at synapses. They can also activate immune system cells that cause inflammation and devour deficient cells.[16] Neurofibrillary braids are braided strands of insoluble proteins in the nerve cell (Figure 2). Increased levels of tau: An abnormal protein component of neurofibrillary braids and beta-amyloid.[17] The formation of beta-amyloid protein plaques and Gross Anatomy of Alzheimer's Brain can be seen in Figure 3 & 4.

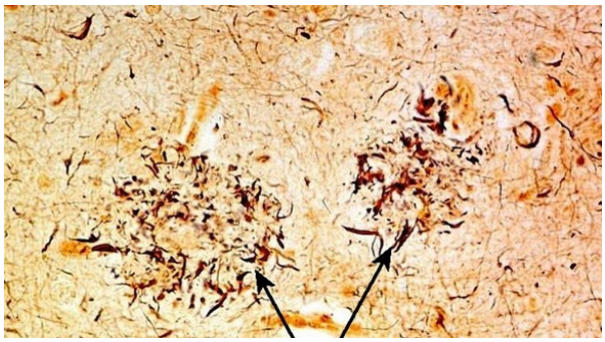

Figure 2 Neurofibrillary braids.

Source: https://www.britannica.com/science/Alzheimer-disease#ref107060.

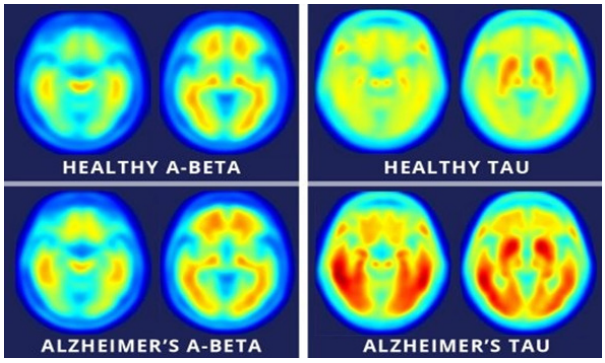

Figure 3 CT scan of a normal brain compared to a brain with Beta-Amyloid plaques.

Source: Anti-agingfirewalls.com/2014/08/15/the-amyloid-beta-face-of-alzheimers-disease.

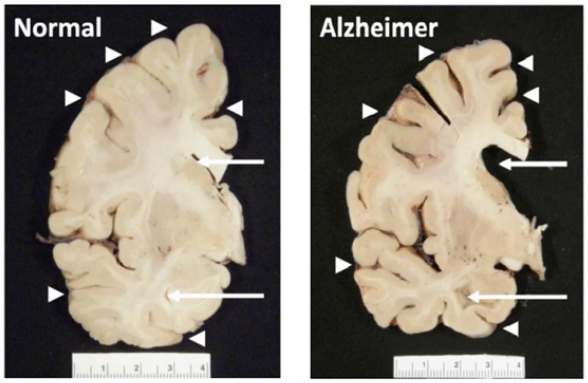

Figure 4 Gross Anatomy of Alzheimer's Brain.

Source: Molecularneurodegeneration.biomedcentral.com/articles.

Casella Filho et al.[18] defines a marker as a measurable variable found in a biological sample, such as blood, or detected by imaging, which is capable of predicting the pathophysiology of a disease and can also be used as a response to therapeutic interventions. Markers, when analyzed and properly measured through clinical analysis, serve as laboratory measures capable of reflecting pathogenic processes.[19]

Given the challenge of finding an early diagnosis for AD, researchers have developed numerous biomarkers that identify its pathological aspects. Identifying alterations in the concentrations of central (cerebrospinal fluid) and peripheral (plasma/serum) inflammatory markers has proved to be an efficient strategy in helping to identify early histopathological processes. Doses of Tau (TAU), phosphorylated Tau (pTAU) and amyloid (Aβ) proteins have been identified in cerebrospinal fluid and are considered the most reliable markers of Alzheimer's disease; these proteins reflect Tau and amyloid pathologies. The analysis of these biomarkers makes it possible to diagnose patients with AD at an early stage and even before the development of dementia, as well as differentiating AD from other degenerative dementias.[20]

In vitro studies have shown that the activation of microglia leads to a reduction in the accumulation of β-amyloid protein; however, in order for this process to take place, there is prolonged exposure of the central nervous system (CNS) to the pro-inflammatory cytokines involved in this cascade, which results in neurotoxicity and accelerates the degenerative process.[21] The mechanism of activation of the inflammatory response is not sufficient to contain the aggregation of the β-amyloid peptide and the hyperphosphorylation of the tau protein in situations of neurodegenerative pathologies, and can thus aggravate the disease process due to the triggering of the inflammatory cascade.[22]

The process of inflammation in AD is complex and requires further research in order to be better understood. For this reason, the need to establish the diagnosis of Alzheimer's disease at an early stage has led to studies of safe inflammatory biomarkers capable of identifying the pathological aspects of the disease, as well as its prevention and treatment, since we know that once installed, this disease is irreversible (Figure 5).

Neuroinflammation in Alzheimer's disease

Growing evidence suggests that the pathogenesis of Alzheimer's disease is not restricted to the neuronal compartment, but includes strong interactions with immunological mechanisms in the brain. Inflammation is an acute response of the immune system that can result in increased concentrations of pro-inflammatory cytokines in the circulatory system,

and exposure to these cytokines for a prolonged period appears to be linked to degenerative effects that can predispose to a variety of chronic diseases.[23] Inflammation occurs in response to cell damage as a positive effect, as it is the body's defense response; however, when inflammation is prolonged, it can cause tissue damage.

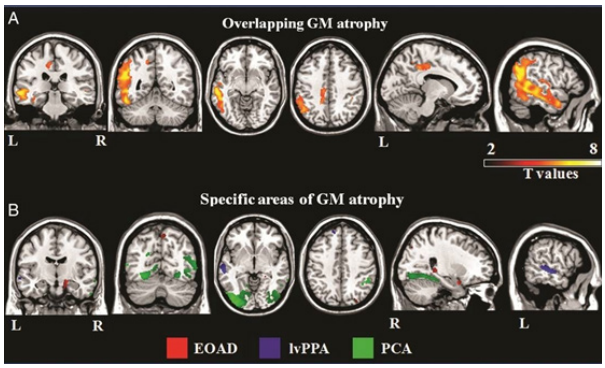

Figure 5 Magnetic resonance images showing the different patterns of damage to the cerebral cortex in atypical forms of Alzheimer's disease.

Source: Radiological Society of North America.

In response to the damage caused by the histopathological signs of AD, especially by the deposition of amyloid protein, glial cells are activated and pro-inflammatory cytokines are produced. In the long term, this is a pathway involved in the neurodegenerative process that can intensify the degenerative process, contributing to the pathological process of Alzheimer's disease.[24]

Although it is known that the activation of glial cells and the production of pro-inflammatory cytokines are related to neurodegenerative processes, the mechanisms for inhibiting the production of pro-inflammatory cytokines and reducing the degenerative damage that occurs as a result of the overactivation of glial cells through physical exercise remain inconclusive.[25,26] A possible explanation for this pathway may be linked to the interleukin 6 (IL-6) protein, which is synthesized by muscle cells during muscle contraction and promotes the release of cytokines that modulate metabolic processes in other tissues.[27]

Physical activity and inflammatory markers

The benefits of physical exercise in reducing low-grade inflammation and improving cognitive function has become a growing field of interest. Epidemiological research has shown that a sedentary lifestyle intensifies the processes of disability and dependence, and also increases the incidence of chronic diseases.[28]

According to Nunes and Dall'Ago,[29] physical exercise has been inversely associated with high levels of different inflammatory markers. It plays a neurotrophic role, capable of promoting a reduction in the accumulation of β-amyloid peptide and the hyperphosphorylation of tau protein, being an important alternative pathway for reducing the degenerative process, which does not result in the release of pro-inflammatory factors,[30] as well as helping to reduce the levels of pro-inflammatory cytokines and improving peripheral concentrations of BNDF.[31]

Exercise can be considered an anti-inflammatory factor, as it inhibits the production of pro-inflammatory factors such as TNF-α and IL-1B, stimulates the production of IL-1ra and IL-10, in addition to inducing the release of soluble TNF-α receptors and also the expression of various proteins with anti-inflammatory properties, in the long term it can provide an anti-inflammatory response, which is mediated by IL-6 derived from skeletal muscle.[32]

Thus, the regular practice of physical exercise is capable of inducing mechanisms that delay and/or prevent the development of numerous chronic and degenerative diseases, including AD, and is therefore a factor of great relevance for research, as it contributes to maintaining and improving physical and functional fitness in general, as well as promoting an increase in longevity. Bullain et al.[33] carried out a longitudinal epidemiological study in which the aim was to assess the correlation between cognitive functions and functional capacity in long-lived elderly people. As a result, they found a high correlation between low physical performance, suggesting that dementia can not only affect cognitive functions, but also functional capacity, which justifies that physical performance can interfere with this variable.

Voss et al.[34] analyzed how a randomized aerobic exercise program carried out over one year with 65 healthy elderly people with an average age of 66 could affect serum levels of brain-derived neurotrophic factor (BDNF), markers of type 1 growth factor (IGF-1), and vascular endothelial growth factor (VEGF). It was also analyzed whether the change in the concentration of these growth factors was associated with changes in functional connectivity through exercise, and the extent to which pre-intervention growth factor levels were associated with training-related changes in functional connectivity. At the end of the interventions, the results showed that although there were no changes in the level of growth factors, greater temporal lobe connectivity between the bilateral parahippocampus and the bilateral middle temporal gyrus was associated with an increase in BDNF, IGF-1 and VEGF in the group that underwent the aerobic exercise program; however, these results were not found in the control group.

Liang et al.[35] carried out a study in which 69 elderly people (17 men, 52 women) aged between 55 and 88, all of whom were cognitively normal, were recruited by the Washington University Alzheimer's Disease Research Center. The aim of the research was to show the association between physical exercise and Alzheimer's disease in humans using imaging and central biomarkers from cerebrospinal fluid (Pittsburgh Compound B (PIB), β-amyloid (Aβ), tau, and phosphorylated tau (ptau).

The data was cross-referenced with a questionnaire on levels of physical exercise over the last decade. The results showed that there was a significant difference between physically active individuals with regard to the load of amyloid protein assessed by neuroimaging (p=.030), as well as the concentrations of tau protein (p=.040) and ptau (p=.044). The results were similar for GDP after control for co-variables; tau (p = 0.115) and phospho-Tau (p= 0.123) differences were reduced to non-significant trends. Further analysis also showed that active individuals who exercise within the norms set by the American Heart Association (30 minutes of moderate exercise 5 days a week) had significantly lower PIB and higher levels of β-amyloid with and without controlling for co-variables (PIB: p = .006 and p =. 001; Aβ: p =.042 and p =.046).

It is concluded that these results are in favor of an association between physical exercise and biomarkers of Alzheimer's disease, this research suggests that physical exercise may have beneficial effects on AD, the analysis of exercise graphs in relation to biomarker levels suggests a strong association that physical exercise interferes with biomarkers, including amyloid deposition measured with levels of Aβ, tau, phospho-Tau in cognitively normal elderly.[36–40]

Nascimento et al.[31] in a study aimed to analyze the effects of a multimodal physical exercise program on peripheral brain-derived neurotrophic factor (BDNF) levels and cognitive functions in elderly individuals with mild cognitive impairment (MCI). Participants were genotyped for the BDNF polymorphism and cognitive functions were analyzed by the Montreal Cognitive Assessment (MoCA) before and

after the intervention. A total of 45 people took part in the study and were divided into control and trained groups. The trained group participated in multimodal physical training for a period of 16 weeks. The results showed a significant interaction between subjects ($p < 0.05$), which indicates a beneficial contribution to cognitive functions, independent of genotype. However, only participants with (BDNF-met) genotypes showed significant improvements in peripheral BDNF levels. The results showed that the BDNF genotype seems to modulate the effects of physical exercise on BDNF secretion, but there are probably alternative pathways involved in improving cognition that are stimulated by exercise. We can therefore conclude from this study that the 16-week multimodal physical exercise program improved peripheral BDNF levels and cognitive function in the elderly, that non-carriers of the BDNF Met. allele showed more marked and significant improvements in peripheral BDNF levels after the 16-week exercise program compared to carriers of the BDNF Met. allele, In addition, there were cognitive improvements independent of genotype and the induced exercise program significantly improved the lipid profile for both groups, non-carriers and carriers of the BDNF Met. allele.

Nascimento et al.[31] in another study, where the objective was to analyze the effects of a 16-week multimodal physical exercise program on peripheral BDNF levels and on Tumor Necrosis Factor (TNF), interleukin-6 (IL-6) as pro-inflammatory markers with 30 cognitively healthy elderly and 37 with mild cognitive disorder (MCI) who were part of the control group (CG) and trained groups (TG). The results showed a significant interaction between the subjects, which indicates the beneficial contribution in reducing TNF, IL-6 and improving BDNF, as well as cognitive functions that also showed improvements for the MCI trained group, and it can be concluded that physical exercise was effective in reducing pro-inflammatory cytokines and improving peripheral levels of BDNF, with positive effects on cognition.

Hoffmann et al.[41] conducted a study to evaluate the effects of a moderate to high intensity aerobic exercise program in patients with mild AD. The analysis was carried out using a randomized controlled trial, in which 200 patients diagnosed with mild Alzheimer's disease and a control group took part. The exercise sessions were supervised and carried out for 16 weeks, three times a week, for 60 minutes. The result showed that neuropsychiatric symptoms decreased significantly, and there was also a possible effect on cognition, which suggests that physical exercise can influence this result.

Morris et al.[42] carried out a randomized study on the effect of 26 weeks of a supervised aerobic exercise program on memory, executive function, functional capacity and depression in early AD, compared to non-aerobic stretching and toning training, 68 elderly people participated in the study. Aerobic exercise showed a significant gain in functional capacity compared to the second group. There was no clear effect on memory benefits, executive function or depressive symptoms. However, the results showed an improvement in cardiorespiratory fitness, which in turn was positively correlated with changes in memory performance and bilateral hippocampus volume.[43]

Final considerations

According to this study, it can be concluded that the regular and systematic practice of physical exercise seems to help protect against inflammatory mediators that promote the progression of Alzheimer's disease (AD). This practice may also result in improvements in the preservation of cognitive functions in patients with AD, in the reduction of neuropsychiatric symptoms, in the improvement of functional and cardiorespiratory capacity, as well as increasing longevity.

Despite the many studies that have helped to elucidate the inflammatory mechanisms associated with AD, there are still gaps to be filled. In particular, there is a need to better understand the mechanisms for inhibiting the production of pro-inflammatory cytokines and reducing the degenerative damage caused by the overactivation of glial cells through physical exercise. In addition, it is necessary to detail exercise programs, including intensity, frequency and duration appropriate for the practice of systematized physical activity in this population. These issues highlight the need for further research on the subject, aimed at filling these gaps and providing a more complete understanding of the role of physical exercise in the prevention and treatment of AD.

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Conflicts of interset

The authors declare no conflicts of interset.

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