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Physical Exercise as a Strategy for Prevention and Management of Alzheimer's Disease Progression

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ABSTRACT

Background: Alzheimer's disease (AD, Alzheimer's Disease) is a chronic, progressive neurodegenerative disease that is a major cause of dementia in the elderly. Current drug therapies have limited effectiveness, prompting the search for alternative and complementary treatments. A growing body of scientific evidence suggests that regular physical activity may play a key role in preventing and slowing the progression of AD by affecting brain fitness

Purpose: The purpose of this study is to analyze the available scientific evidence and examine the impact of physical activity on the progression, course and prevention of AD.

We analyze how regular exercise may affect cognitive function, brain structure and neurodegenerative biomarkers associated with AD.

Material and methods: The review was based on the analysis of materials collected in the databases "Pubmed", Google Scholar, ResearchGate, books and other scientific articles. The search was conducted using keywords: “Alzheimer’s Disease”, “physical activity”, “impact of PA on AD”, “prevention”

Results: A review of the literature has shown that regular physical activity can help improve cognitive function and delay the progression of AD through a variety of biological mechanisms, including increased neurogenesis, improved cerebral blood flow and reduced inflammation.

Conclusions: The results suggest that regular physical activity may play an important role in the prevention and progression of AD, offering potential cognitive and neuroprotective benefits. These findings the importance of promoting physical activity as a non-pharmacological strategy to counteract AD. Based on these findings, further research should focus on determining the optimal types and intensities of exercise and the mechanisms behind their effects.

Key words: Alzheimer’s disease, Alzheimer’s disease and physical activity, influence of physical activity on AD, prevention

Introduction: Alzheimer's disease (AD, Alzheimer's Disease) is one of the most devastating neurodegenerative diseases that affects millions of people worldwide.

Alzheimer’s disease (AD) is the most common type of dementia and one of the most frequent neurodegenerative pathologies in elderly people, constituting about 90% of the cases of dementia in this population [3,16].

Since it was first described by Alois Alzheimer in 1907, it has become one of the major health and social challenges of the 21st century[29]. AD is characterized by progressive memory problems, disorientation and impaired daily functioning that eventually lead to total dependence on the care of others. As populations around the world age, the number of people affected by the disease is expected to increase significantly in the coming decades, posing an urgent challenge to researchers, clinicians and policymakers to find effective prevention and treatment strategies for the disease [16,20].

To date, AD research has mainly focused on pharmacological aspects aimed at slowing the progression of the disease by modifying pathological processes such as beta-amyloid

and tau protein accumulation in the brain. Although these approaches have some benefit, their efficacy is limited, and the search for alternative and complementary methods of treatment and prevention is growing in importance [15,16,20].

One area that is gaining increasing attention is the role of physical activity (PA) in the context of AD. Epidemiological and intervention studies suggest that regular physical activity may play a key role in preventing and slowing the progression of AD [23]. During the last decade, physical activity (PA) has been identifed as one of the main modifable factors that afects the development of AD pathophysiology [21].

Not only is physical activity an important part of a healthy lifestyle, but it also benefits brain health through a number of biological mechanisms, such as improving blood flow, neurogenesis, reducing inflammation and modifying the energy metabolism of nerve cells[14,15].

Physical activity is increasingly being proposed as an inexpensive and low-risk adjunctive therapy for patients with Alzheimer's disease. Numerous systematic reviews and meta-analyses conducted in recent years have evaluated the association between regular physical activity and the risk of developing AD pathology, as well as its impact on disease progression in people who already have the disease [7]

These studies show that regular exercise can delay the onset of cognitive impairment and functional decline in AD patients. They work by improving brain health, promoting neuroplasticity and reducing AD-related risk factors. These mechanisms make PA a promising approach for managing AD, with the potential to alleviate symptoms and slow the progression of the disease[22,25].

In light of the growing number of AD cases and the limitations of current therapies, identifying and promoting effective non-pharmacological strategies, such as physical activity, becomes crucial. The results of this study may not only contribute to a better understanding of the role of physical activity in the context of AD, but also provide valuable insights for clinicians, caregivers and patients themselves in their daily lives and treatment planning [5,13].

Pathophysiology

The pathophysiology of AD is complex and multifactorial, involving several key pathological processes that lead to neurodegeneration and loss of brain function. The main characteristics of AD are the accumulation of beta-amyloid in the form of amyloid plaques and hyperphosphorylation of tau protein, leading to the formation of neurofibrillary tangles.

Moreover Patients with AD have low blood and brain BDNF levels from the early stages of the disease, and BDNF levels are positively correlated with cognitive function [3,10,31].

Beta-amyloid accumulation

Beta-amyloid is a protein fragment derived from the larger amyloid precursor protein (APP). Under pathological conditions, APP is abnormally cut by beta- and gamma-secretase enzymes, leading to the formation of beta-amyloid. These beta-amyloid peptides (mainly Aβ42) are hydrophobic and tend to aggregate, forming insoluble amyloid plaques in the extracellular space of neurons. These plaques interfere with communication between brain cells, induce inflammation and lead to neuronal death through various mechanisms, including activation of microglia and oxidative stress [10,16].

Hyperphosphorylation of the tau protein

The second key pathological process in AD is abnormal phosphorylation of the tau protein. In a healthy brain, tau helps stabilize microtubules, which are essential for cellular transport in neurons. In AD, tau becomes over-phosphorylated, leading to its dissociation from microtubules and intracellular aggregation in the form of neurofibrillary tangles.
These tangles disrupt the structure and function of neurons, causing their degeneration and death. This process is particularly damaging in the hippocampus, an area of the brain crucial for memory and spatial orientation [10,16].

Dysfunction of the cholinergic system

As AD progresses, there is also a significant loss of cholinergic neurons, particularly in the basal nucleus Meynert region, leading to deficits in cholinergic neurotransmission. Deficiency of acetylcholine, a neurotransmitter crucial to memory and attention processes, is one of the early symptoms of AD and is the target of many pharmacological interventions [3].

Inflammatory processes and oxidative stress

In addition to the main pathologies associated with beta-amyloid and tau, AD is also characterized by chronic inflammation and oxidative stress. Activation of microglia, the brain's immune response to pathological changes, leads to the secretion of pro-inflammatory cytokines that can potentiate neuronal damage . At the same time, oxidative stress, caused by excessive production of free radicals, leads to damage to lipids, proteins and DNA, contributing to further degeneration of neurons [3,10,13,16].

Metabolic and mitochondrial disorders

Mitochondrial dysfunction, which is crucial for cellular energy production, is also observed in AD. Mitochondrial dysfunction leads to decreased ATP production and increased production of reactive oxygen species (ROS), which further exacerbates oxidative stress and cellular damage . In addition, the brains of AD patients often exhibit changes in glucose metabolism, which can contribute to neuronal dysfunction and worsening of the disease [3,10,13].

Triggering the neurodegenerative cascade

The combination of these pathological processes leads to loss of neurons and synapses, reduced brain mass and cognitive impairment. Progressive neurodegeneration in AD results in characteristic changes in brain structure, including atrophy in areas such as the hippocampus, frontal and temporal cortex, which are crucial for memory and cognitive functions [3,10,26].

Epidemiology of Alzheimer's disease

Alzheimer's disease (AD) is the most common form of dementia worldwide, currently affecting approximately 50 million people. The prevalence of AD is expected to rise significantly due to global population aging. Epidemiological studies indicate that the number of individuals affected by Alzheimer's and other dementias is projected to triple, reaching 152 million by 2050. This dramatic increase is anticipated to exert immense pressure on healthcare systems, especially in low- and middle-income countries where resources are already constrained. Addressing this growing public health challenge requires effective strategies and policies focusing on prevention, early detection, and adequate care infrastructur [15,16,29].

Prevalence and risk factors

The incidence of AD increases dramatically with age. The disease affects about 5% of people aged 65-74, and the risk rises to more than 30% in people older than 85 . Women are more likely to develop AD than men, which partly explains their longer life expectancy, but biological and hormonal differences may also play a role .Genetics also play a key role in the epidemiology of AD. Mutations in the APP, PSEN1 and PSEN2 genes are associated with early disease onset, although they account for less than 1% of all cases . The best-known risk gene for late-onset AD is APOE ε4, whose presence increases the risk of developing the disease, with homozygous carriers having up to a 12-fold higher risk [3,5,16,18,].

Environmental and lifestyle factors

In addition to genetic factors, lifestyle and environmental factors also affect the risk of developing AD. Chronic diseases such as type 2 diabetes, hypertension and obesity are associated with a higher risk of dementia . In contrast, physical activity, a healthy diet, maintaining cardiovascular health and cognitive activity are thought to be protective against AD[30] . Studies suggest that about one-third of AD cases can be attributed to modifiable risk factors, opening up prospects for preventive strategies [3,5,18].

Socio-economic impact

The increase in the number of AD cases has a huge socioeconomic impact. The costs associated with caring for people with dementia are significant, both direct (medical and care costs) and indirect (lost wages for caregivers). In 2019, the global cost of dementia was more than $1 trillion and it is projected that it could rise to $2 trillion by 2030 [16,25,27].

Impact of physical activity on the prevention, course and treatment of Alzheimer's disease:

A growing body of research indicates that physical activity (PA) can play an important role in preventing, slowing the course of, and supporting the treatment of AD. Regular exercise affects brain function at multiple levels, from molecular mechanisms to structural and functional changes, with significant implications for patients at risk of AD and those who are already developing the disease [16].

Prevention

The importance of physical activity in AD prevention is supported by numerous epidemiological studies. A meta-analysis by Sofi et al. (2011) involving 15 studies and more than 33,000 participants, found that people with active lifestyles had a 38% lower risk of developing AD compared to those who were physically inactive[19,25]. A study by Hamer and Chida (2009) also confirmed that regular exercise can reduce the risk of AD by up to 45%.

Recent research strongly supports the role of regular physical activity (PA) in significantly reducing the risk of developing Alzheimer's disease (AD). A comprehensive meta-analysis that pooled data from 16 studies, encompassing over 160,000 participants, found that

individuals who engage in regular physical activity have a 45% lower risk of developing AD[29].

Similarly, a study that followed 716 older adults over 3.5 years revealed that those with lower levels of daily physical activity were 53% more likely to develop AD compared to their more active counterparts[16] .

On cognitive scales such as the Mini-Mental State Examination (MMSE) and the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog), physical activity has been shown to result in modest but significant improvements[4]. Specifically, Groot et al. (2016) found that aerobic exercise interventions led to better cognitive function in patients with mild to moderate AD, with notable enhancements in memory and executive functions as measured by these scales [31].

Research indicates that aerobic exercise can significantly enhance physical functioning in individuals with Alzheimer's disease (AD). Beyond the physical benefits, aerobic activities have been found to alleviate various behavioral and psychological symptoms associated with dementia. Furthermore, aerobic exercise is generally well-tolerated by older adults with AD, presenting a minimal risk of adverse effects [7,8].

Furthermore, recent meta-analyses reveal that consistent physical activity or exercise has a beneficial impact on hippocampal volume in humans. These studies show that regular engagement in physical activity can help maintain or even increase hippocampal size, counteracting the natural decline in volume that typically occurs with aging [28].

These findings highlight the critical importance of maintaining regular physical activity as a simple and effective strategy to mitigate the risk of AD, emphasizing its potential as a preventive measure in the fight against this debilitating disease [24].

Treatment

Although AD is a neurodegenerative disease for which there is currently no effective drug, PA can aid in the treatment and management of the disease. Clinical studies show that regular exercise can provide behavioral and psychological benefits, as well as improve independence, which is particularly important in the management of AD [6].

Biological mechanisms

The benefits of PA for patients with AD stem from a number of biological mechanisms. First, exercise increases neuroplasticity and neurogenesis It is documented that physical activity stimulates the growth of neurons in the hippocampus, a structure crucial to memory that degenerates in the early stages of AD [2].

In addition, PA affects metabolic pathways and inflammation. Studies indicate that regular exercise can reduce oxidative stress and inflammation in the brain, which may limit neuronal damage and promote repair processes [11]. Exercise also improves insulin sensitivity and glucose metabolism in the brain, which may counteract pathological processes associated with AD [20].

Another key mechanism is the effect of PA on amyloid and tau pathology. Studies in animal models of AD have shown that regular physical activity reduces beta-amyloid deposition and tau hyperphosphorylation, which are key neuropathological features of AD (Adlard et al., 2005)[32].

Furthermore protective mechanisms associated with PA include a reduction in cardiovascular risk factors such as hypertension, diabetes and obesity, which are also associated with a higher risk of developing AD. In addition, physical activity improves cerebral perfusion, which can protect neurons from damage [1].

Prognosis

Engaging in regular physical activity offers substantial prognostic benefits for individuals with Alzheimer's disease (AD). Such activity not only helps delay the progression to the point where institutional care becomes necessary but also supports both mental and physical well-being, especially in the later stages of the disease. This improvement in overall health and quality of life is critical as AD advances. Moreover, physical activity can alleviate some of the stress experienced by caregivers, thereby providing significant social and economic advantages [17].

Disussion:

The impact of physical activity on the prevention and progression of Alzheimer's disease (AD) has been extensively studied, with mounting evidence supporting its beneficial effects. Physical activity appears to play a crucial role in reducing the risk of developing AD

and in attenuating the severity of its symptoms in diagnosed individuals. Mechanistically, regular physical exercise is thought to enhance brain plasticity, reduce neuroinflammation, and improve cerebral blood flow, all of which contribute to neuroprotection and cognitive resilience[7]. Longitudinal studies have shown that midlife physical activity is associated with a decreased risk of AD in later life [6].

The underlying biological mechanisms are multifaceted. Exercise-induced upregulation of neurotrophic factors such as brain-derived neurotrophic factor (BDNF) promotes neuronal growth and synaptic plasticity [12]. Additionally, physical activity mitigates oxidative stress and inflammation, both of which are implicated in AD pathogenesis [13]. Furthermore, enhanced cardiovascular fitness resulting from regular exercise improves cerebral perfusion, which is critical in maintaining neuronal health and function [7].

Clinical trials also support the cognitive benefits of exercise in AD patients. A randomized controlled trial by Lautenschlager et al. (2008) found that a 24-week physical activity intervention significantly improved cognitive function in older adults with mild cognitive impairment (MCI), a precursor to AD[28]. Moreover, aerobic exercise has been shown to increase hippocampal volume, a region critically affected in AD, thereby potentially slowing disease progression [7].

Despite these promising findings, there remain gaps in our understanding. The optimal type, intensity, and duration of physical activity required to confer neuroprotection against AD are yet to be definitively established[4]. Additionally, individual variations in response to exercise, influenced by genetic and environmental factors, necessitate further investigation. Future research should aim to elucidate these parameters and explore the molecular pathways by which physical activity exerts its protective effects.

Conclussion:

In conclusion, physical activity emerges as a potent modifiable risk factor for AD, with robust evidence supporting its role in both prevention and management of the disease. Integrating regular physical exercise into lifestyle interventions holds promise for mitigating the global burden of AD, highlighting the need for public health strategies to promote physical activity across all age groups[7].

Implementing lifestyle changes in the early stages of Alzheimer's disease, including presymptomatic and predementia phases, could potentially delay up to one-third of dementia cases globally. Regular physical activity (PA) plays a critical role in this process by influencing several biological mechanisms. It helps regulate amyloid-beta (Aβ) turnover, reduces inflammation, enhances the production and release of neurotrophins, and improves cerebral blood flow (CBF). Consequently, it is advisable to incorporate multimodal interventions that encourage an active lifestyle for the elderly[9].

Physical exercise offers numerous benefits that impact Alzheimer's disease through various mechanisms[27]. These range from mitigating associated risk factors to supporting overall brain health and function. Promoting an active lifestyle is thus a key strategy in the management and prevention of Alzheimer's disease[31].

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