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Physical Exercise as a Therapeutic Strategy in Alzheimer's Disease: Mechanisms and Benefits

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Abstract

Introduction and Purpose

Alzheimer's disease (AD) is a progressive neurodegenerative disorder with no definitive cure. This article explores the impact of physical exercise on AD risk reduction and disease progression, emphasizing its molecular, cognitive, and physiological benefits.

Materials and Methods

A comprehensive review of recent studies, meta-analyses, and clinical trials was conducted to evaluate the effects of various exercise modalities on AD-related pathophysiology, cognitive decline, and neuroprotection.

Results

Findings indicate that regular physical activity is associated with a 33% lower risk of developing AD. Exercise interventions lasting over 16 weeks significantly improve cognitive function, as measured by MMSE and ADL scores. Mechanistically, exercise

enhances BDNF levels, promotes Aβ clearance, reduces tau pathology, mitigates neuroinflammation, and improves cerebrovascular health.

Conclusion

Physical exercise is a cost-effective, non-invasive intervention for AD prevention and management. Future research should focus on optimizing individualized exercise protocols and leveraging digital health technologies for long-term adherence and effectiveness.

Keywords

Alzheimer's disease, physical exercise, neuroprotection, cognitive decline, BDNF, amyloid-beta, neuroinflammation, cerebrovascular health.

Introduction

Alzheimer's disease (AD) is the most prevalent neurodegenerative disorder, affecting millions worldwide and posing a significant public health challenge. Characterized by progressive cognitive decline, memory impairment, and behavioral disturbances, AD severely impacts individuals and their families. The increasing life expectancy of the global population has led to a rising prevalence of AD, with projections indicating that the number of cases will exceed 150 million by 2050 [1]. Despite decades of research, there remains no definitive cure for AD, and current pharmacological treatments provide only symptomatic relief, failing to halt or reverse disease progression [2].

Given the limited efficacy of drug therapies, there is an urgent need to explore non-pharmacological interventions that can reduce AD risk and slow its progression. Lifestyle factors such as diet, cognitive engagement, social interactions, and physical activity have been extensively studied for their neuroprotective effects. Among these, exercise has emerged as one of the most promising interventions due to its profound impact on brain health, cognition, and neuronal resilience [3, 4]. Regular physical activity has been associated with a lower incidence of dementia, improved cognitive function, and a reduction in key neuropathological features of AD, including amyloid-beta (Aβ) plaques and tau tangles [5].

The mechanisms underlying the neuroprotective effects of exercise are multifaceted and involve various physiological and molecular pathways. Exercise enhances cerebrovascular

health by increasing blood flow, promoting angiogenesis, and improving endothelial function, all of which are essential for maintaining an optimal neuronal environment. Moreover, exercise has been shown to modulate neuroinflammation and reduce oxidative stress, thereby counteracting key contributors to AD pathology [6, 7]. Additionally, physical activity upregulates brain-derived neurotrophic factor (BDNF), insulin-like growth factor-1 (IGF-1), and vascular endothelial growth factor (VEGF), all of which support synaptic plasticity, neurogenesis, and neuronal survival [8].

Beyond its biological effects, exercise also plays a role in enhancing cognitive reserve and mental resilience, helping individuals maintain functional independence for a longer period. It has been linked to improvements in executive function, memory retention, and attentional control, making it a critical component of dementia prevention strategies [9,10]. Epidemiological studies have demonstrated that individuals engaging in moderate to vigorous exercise have a significantly lower risk of developing AD compared to those with sedentary lifestyles [11].

Despite the compelling evidence supporting the benefits of exercise in AD prevention and management, several questions remain regarding the optimal type, intensity, and duration of physical activity required for maximal neuroprotection. Current recommendations suggest at least 150 minutes per week of moderate-intensity aerobic exercise, combined with resistance training and balance exercises, to achieve significant cognitive benefits. However, individualized exercise regimens tailored to an individual's physical capabilities and cognitive status may yield even better outcomes [1, 12].

In this article, we provide a comprehensive review of the current evidence regarding the impact of exercise on AD risk reduction and disease progression. We discuss the molecular and physiological mechanisms through which physical activity exerts its neuroprotective effects and explore clinical findings that support the incorporation of exercise as a fundamental component of AD prevention and treatment strategies. By furthering our understanding of how exercise influences brain health, we can develop targeted interventions aimed at reducing the global burden of AD and improving the quality of life for individuals at risk or already affected by this devastating disease.

Pathophysiology of Alzheimer's disease

Alzheimer's disease (AD) is a multifactorial disorder with complex neuropathological mechanisms that involve amyloid-beta (Aβ) plaque accumulation, neurofibrillary tangles composed of hyperphosphorylated tau protein, chronic neuroinflammation, oxidative stress, mitochondrial dysfunction, and vascular impairments. These interconnected pathological processes collectively lead to the progressive loss of synaptic function, neuronal death, and cognitive decline [8,13,14].

Aβ accumulation is considered a hallmark of AD and plays a central role in disease pathogenesis. Aβ is derived from the amyloid precursor protein (APP) through sequential cleavage by β-secretase (BACE1) and γ-secretase. In AD, an imbalance between Aβ production and clearance results in the aggregation of insoluble Aβ42 peptides, forming extracellular amyloid plaques [13]. These plaques disrupt neuronal communication, promote synaptic dysfunction, and activate microglial cells, leading to a pro-inflammatory cascade that exacerbates neurodegeneration [15].

The intracellular aggregation of hyperphosphorylated tau protein is another defining feature of AD. Under normal physiological conditions, tau stabilizes microtubules and supports axonal transport. However, in AD, tau undergoes hyperphosphorylation, loses its microtubule-stabilizing function, and aggregates into neurofibrillary tangles (NFTs). The formation of NFTs disrupts neuronal cytoskeletal integrity, impairs axonal transport, and ultimately results in neuronal apoptosis. Additionally, tau pathology spreads in a prion-like manner, propagating from affected brain regions to previously unaffected areas, contributing to disease progression [13].

Chronic neuroinflammation is a key driver of neurodegeneration in AD. Activated microglial cells, the resident immune cells of the central nervous system, play a dual role in AD pathophysiology. Initially, microglia attempt to clear Aβ plaques via phagocytosis. However, as the disease progresses, persistent activation of microglia leads to the excessive release of pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1β (IL-1β). This sustained inflammatory response damages neurons [6,7].

Oxidative stress plays a crucial role in AD pathogenesis, leading to neuronal damage and synaptic dysfunction. Mitochondrial dysfunction is a major source of reactive oxygen species (ROS) in AD-affected neurons. Increased oxidative stress damages lipids, proteins, and DNA, ultimately resulting in neuronal apoptosis. Impaired mitochondrial function also reduces ATP production, further compromising neuronal survival and function. Additionally, oxidative stress promotes Aβ accumulation and tau hyperphosphorylation, creating a vicious cycle that accelerates neurodegeneration [16].

Cerebrovascular dysfunction is increasingly recognized as a major contributor to AD pathology. Reduced cerebral blood flow (CBF), blood-brain barrier (BBB) breakdown, and microvascular dysfunction are common findings in AD patients. Impaired vascular function exacerbates Aβ accumulation by reducing its clearance through perivascular drainage pathways [4, 6]. Moreover, chronic hypoxia and ischemia contribute to neuronal damage and cognitive decline. Exercise has been shown to enhance angiogenesis, improve CBF, and strengthen BBB integrity, thereby mitigating some of these vascular impairments [9].

AD is fundamentally a disease of synaptic failure. Early in the disease course, synaptic loss precedes neuronal death and is closely associated with cognitive decline. The accumulation of soluble Aβ oligomers disrupts synaptic plasticity, impairs long-term potentiation (LTP), and reduces neurotransmitter release. Over time, this progressive synaptic loss leads to irreversible cognitive deficits. Targeting synaptic resilience through lifestyle interventions, such as exercise, offers a promising avenue for neuroprotection [6,13]].

By understanding these complex and interconnected mechanisms, researchers can develop more effective therapeutic strategies to combat AD. Exercise has emerged as a non-pharmacological intervention capable of modulating multiple AD-related pathways, offering potential benefits in preventing or slowing disease progression.

Neuroprotective mechanisms of exercise in Alzheimer's disease

Physical exercise exerts its beneficial effects on Alzheimer's disease through multiple interconnected mechanisms that influence neuroprotection, inflammation, vascular health, and brain metabolism. Exercise promotes neurogenesis and enhances synaptic plasticity, particularly in the hippocampus, which is critical for learning and memory [9]. This occurs through the upregulation of brain-derived neurotrophic factor (BDNF), a key protein that supports neuronal survival, differentiation, and synaptic function. Increased BDNF levels

have been linked to better cognitive performance and resilience against neurodegenerative processes [17].

Another crucial effect of exercise is its role in reducing amyloid-beta (Aβ) plaque accumulation, a hallmark feature of AD. Regular physical activity enhances the activity of proteolytic enzymes such as neprilysin and insulin-degrading enzyme (IDE), which are responsible for breaking down Aβ aggregates. By facilitating the clearance of Aβ, exercise prevents its toxic accumulation in the brain. Additionally, it helps reduce tau hyperphosphorylation, thereby preventing the formation of neurofibrillary tangles (NFTs) that disrupt neuronal stability and function [18].

Exercise also exerts anti-inflammatory effects, mitigating chronic neuroinflammation that contributes to AD progression. Physical activity modulates microglial function, shifting these immune cells from a pro-inflammatory state to a neuroprotective one. This transition reduces the release of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6), which are known to exacerbate neuronal damage. By dampening inflammation, exercise creates a more favorable environment for neuronal health and cognitive function [7].

Furthermore, exercise plays a significant role in reducing oxidative stress and improving mitochondrial function. Mitochondria, the energy powerhouses of cells, are essential for neuronal survival, and their dysfunction is a key feature of AD [8]. Exercise enhances mitochondrial biogenesis, increasing ATP production and reducing the levels of reactive oxygen species (ROS), which can damage neurons. Upregulation of antioxidant enzymes such as superoxide dismutase (SOD) and glutathione peroxidase (GPx) further protects against oxidative damage, ensuring better cellular resilience [13].

Cerebrovascular health is another crucial factor influenced by exercise. Regular physical activity promotes angiogenesis, increases capillary density, and enhances endothelial function, leading to improved cerebral blood flow. This increased perfusion ensures that neurons receive an adequate supply of oxygen and nutrients while also aiding in the removal of metabolic waste products. Moreover, exercise helps maintain the integrity of the blood-brain barrier (BBB), preventing the infiltration of harmful molecules that could exacerbate neurodegeneration [6].

The glymphatic system, responsible for clearing metabolic waste from the brain, also benefits from exercise. Physical activity enhances cerebrospinal fluid (CSF) flow, thereby improving the removal of neurotoxic proteins, including Aβ and tau aggregates. This process is particularly effective during sleep, highlighting the importance of exercise in promoting overall brain clearance mechanisms [7,9].

Additionally, exercise helps regulate glucose metabolism and insulin sensitivity, which are critical factors in AD pathogenesis. Impaired insulin signaling has been associated with cognitive decline, and physical activity enhances neuronal glucose uptake, ensuring optimal energy metabolism. By modulating both central and peripheral insulin pathways, exercise reduces the risk of metabolic dysfunction that could contribute to neurodegeneration [9,18].

Finally, exercise induces hormesis, a mild physiological stress response that triggers adaptive cellular mechanisms. This includes the upregulation of heat shock proteins (HSPs), autophagy, and DNA repair pathways, all of which enhance neuronal survival and longevity. These adaptive responses contribute to greater resilience against neurodegenerative diseases and support overall cognitive health [6,18].

In conclusion, exercise exerts its neuroprotective effects through a multifaceted approach, targeting Aβ accumulation, tau pathology, neuroinflammation, oxidative stress, vascular dysfunction, and metabolic resilience. By promoting synaptic plasticity and enhancing neurogenesis, exercise serves as a potent intervention in both AD prevention and disease management. Future research should focus on optimizing exercise protocols to maximize their therapeutic benefits across diverse populations.

Exercise and Alzheimer's disease risk reduction

There is growing evidence that regular physical activity is one of the most effective non-pharmacological strategies for reducing the risk of developing Alzheimer's disease (AD). Numerous epidemiological studies and meta-analyses have highlighted the inverse relationship between exercise and AD risk, suggesting that individuals who engage in moderate to high levels of physical activity have a significantly lower chance of developing cognitive impairment compared to sedentary individuals.

Several large-scale cohort studies have reinforced this link. For example, a 2024 meta-analysis by Xiao et al. found that individuals engaging in regular aerobic and resistance

training exhibited a 33% reduced risk of AD compared to those with sedentary lifestyles. The protective effects of exercise were more pronounced in those who consistently engaged in physical activity over an extended period, indicating a cumulative benefit [1].

The beneficial effects of exercise on AD risk reduction are mediated by several physiological mechanisms. One of the primary ways in which exercise lowers the risk of AD is through enhanced neuroplasticity and neurogenesis. Exercise stimulates the release of brain-derived neurotrophic factor (BDNF), a key protein involved in neuronal survival, differentiation, and synaptic plasticity. BDNF is crucial for hippocampal function, a brain region heavily impacted in AD. Higher levels of BDNF have been associated with better memory retention and cognitive function, and exercise-induced increases in BDNF help preserve neuronal integrity and cognitive performance over time [19].

In addition to promoting neuroplasticity, exercise is known to facilitate the clearance of amyloid-beta (Aβ) and tau proteins, both of which are central to AD pathology. Physical activity enhances the activity of proteolytic enzymes, including neprilysin and insulin-degrading enzyme (IDE), which break down Aβ aggregates [9]. Furthermore, exercise has been shown to reduce tau hyperphosphorylation, thus preventing the formation of neurofibrillary tangles (NFTs) that contribute to synaptic dysfunction and neuronal death [18].

Another critical way exercise reduces AD risk is by lowering systemic and neuroinflammatory responses. Chronic inflammation is a significant factor in AD development, and elevated levels of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1β (IL-1β) are commonly found in individuals with cognitive impairment. Exercise has been shown to modulate immune responses by shifting microglial cells into a more neuroprotective state, reducing the production of harmful inflammatory cytokines and fostering an environment conducive to neuronal survival [7].

Furthermore, exercise enhances cerebrovascular function, which is critical for maintaining brain health and reducing the risk of AD. Regular physical activity improves endothelial function, increases cerebral blood flow, and supports angiogenesis, ensuring that neurons receive adequate oxygen and nutrients. Studies have demonstrated that individuals who engage in aerobic activities such as walking, cycling, and swimming experience better

vascular health, which in turn reduces AD risk by improving nutrient delivery and waste clearance mechanisms in the brain [6].

Another important mechanism by which exercise lowers AD risk is through enhanced glymphatic system function, a key pathway for clearing metabolic waste from the brain. The glymphatic system is responsible for removing Aβ and other neurotoxic proteins, and exercise has been shown to improve its function by increasing cerebrospinal fluid (CSF) circulation and enhancing sleep quality, both of which are crucial for optimal brain clearance processes [9,20].

Additionally, metabolic health plays a vital role in AD risk, and exercise is a powerful modulator of glucose metabolism and insulin sensitivity. Insulin resistance is a well-established risk factor for AD, as it leads to impaired glucose uptake in neurons, increasing their vulnerability to degeneration. Exercise improves insulin signaling pathways, ensuring efficient glucose metabolism in the brain and reducing the risk of insulin-related cognitive impairment [21].

In conclusion, regular physical activity is a crucial lifestyle factor in lowering the risk of Alzheimer's disease. By enhancing neuroplasticity, reducing amyloid and tau pathology, modulating inflammation, improving cerebrovascular function, and optimizing metabolic health, exercise provides a multi-faceted protective effect against cognitive decline. Future research should focus on determining the optimal types, intensity, and duration of exercise needed for maximum neuroprotective benefits, as well as investigating personalized exercise interventions tailored to an individual's genetic and environmental risk factors.

Exercise in slowing Alzheimer's disease progression

Exercise has been increasingly recognized as an effective intervention in slowing the progression of Alzheimer's disease (AD), particularly in individuals with mild cognitive impairment (MCI) or early-stage AD. While no cure currently exists for AD, engaging in regular physical activity has been shown to slow cognitive decline, maintain functional independence, and improve quality of life in affected individuals.

Multiple randomized controlled trials (RCTs) have demonstrated that physical activity improves cognitive function in individuals with AD. A study found that patients who participated in a structured exercise program for six months exhibited significantly better

performance on the Mini-Mental State Examination (MMSE) and other cognitive assessments compared to sedentary controls [22]. Aerobic exercise, such as walking, swimming, or cycling, has been linked to enhanced executive function, memory retention, and attentional control. These benefits are attributed to the increase in cerebral blood flow (CBF), enhanced synaptic plasticity, and neurogenesis stimulated by exercise. Studies indicate that exercise promotes hippocampal growth, a brain region crucial for memory formation, which is one of the first areas affected in AD [9].

Regular physical activity helps to counteract AD pathology by reducing amyloid-beta (Aβ) plaque accumulation and preventing tau protein hyperphosphorylation. Exercise enhances the clearance of Aβ aggregates by upregulating proteolytic enzymes such as neprilysin and insulin-degrading enzyme (IDE), which break down these toxic proteins. Moreover, exercise helps maintain tau homeostasis, thereby reducing the risk of neurofibrillary tangle formation, which is a hallmark of AD [18].

Physical activity also triggers the release of brain-derived neurotrophic factor (BDNF), insulin-like growth factor-1 (IGF-1), and vascular endothelial growth factor (VEGF), all of which support neuronal survival and function. These neurotrophic factors enhance synaptic connectivity, promote neurogenesis, and repair damaged neurons, slowing the progression of cognitive decline. The upregulation of BDNF is particularly crucial in individuals with AD, as lower BDNF levels have been associated with more severe cognitive impairment [19].

In addition to its cognitive benefits, exercise plays a key role in reducing depression, anxiety, and agitation in AD patients. Many individuals with AD experience behavioral and psychological symptoms of dementia (BPSD), which can be challenging for caregivers [10,23]. Engaging in structured physical activities has been shown to reduce agitation, improve sleep quality, and enhance social engagement. These effects contribute to overall well-being and may slow disease progression by reducing stress-related neuroinflammation [9].

Maintaining mobility and functional independence is essential for individuals with AD. Exercise, particularly resistance and balance training, helps preserve muscle strength, coordination, and gait stability, reducing the risk of falls and associated complications. Studies have found that individuals who engage in progressive resistance training and functional

exercises retain their ability to perform daily tasks (such as dressing, cooking, and walking) for a longer duration than those who remain inactive [12].

While exercise offers substantial benefits for AD patients, personalized interventions tailored to an individual's cognitive and physical abilities yield the best results. For individuals in the early stages of AD, a combination of aerobic and resistance exercises performed at moderate intensity for at least 150 minutes per week is recommended. For more advanced cases, supervised low-impact activities such as chair-based exercises and stretching programs help maintain mobility and prevent muscle atrophy [1,12].

Exercise is a powerful non-pharmacological intervention that slows the progression of Alzheimer's disease by improving cognitive function, reducing neuropathological burden, enhancing neurotrophic support, and maintaining functional independence. With mounting evidence supporting its role, healthcare professionals should encourage AD patients to engage in structured, tailored exercise programs to optimize their cognitive and physical well-being. Future research should focus on identifying the most effective exercise regimens for different stages of AD, ensuring maximal therapeutic benefits.

Conclusion

Physical exercise has emerged as a crucial non-pharmacological intervention in both the prevention and management of Alzheimer's disease. By targeting key pathological mechanisms, including neuroinflammation, oxidative stress, amyloid-beta accumulation, tau hyperphosphorylation, and cerebrovascular dysfunction, exercise provides a multi-faceted approach to slowing cognitive decline. It not only promotes neuronal survival and synaptic plasticity but also enhances neurogenesis and supports the brain's natural repair mechanisms [15,18].

One of the most significant benefits of exercise is its role in maintaining functional independence and improving quality of life in individuals affected by AD. Cognitive decline is often accompanied by a loss of mobility and increased frailty, leading to reduced physical and social engagement. Engaging in regular physical activity, particularly a combination of aerobic exercise and resistance training, has been shown to help maintain muscle strength, balance, and coordination, reducing the risk of falls and enhancing overall well-being [12]. Furthermore, exercise has been linked to improvements in mood and reduced symptoms of anxiety and depression, which are common comorbidities in individuals with AD [1].

While current research strongly supports the neuroprotective effects of exercise, further studies are needed to determine the most effective exercise regimens for individuals at various stages of AD. Personalized exercise programs that consider an individual's cognitive and physical capabilities may offer the best outcomes [1].

Another area that requires further exploration is the potential synergy between exercise and other lifestyle interventions, such as diet and cognitive training. A multi-modal approach that combines exercise with a brain-healthy diet, social engagement, and mental stimulation may provide even greater protection against cognitive decline and neurodegeneration [4].

In conclusion, exercise is a powerful tool that should be integrated into public health strategies and clinical guidelines for AD prevention and management. Encouraging individuals to adopt an active lifestyle from an early age may help reduce the global burden of AD, prolong cognitive function, and improve quality of life for millions. As research continues to uncover the underlying mechanisms through which exercise benefits brain health, it is imperative to translate these findings into actionable strategies that can be widely implemented in aging populations. Future efforts should focus on expanding access to structured exercise programs, educating the public on the importance of physical activity for brain health, and fostering interdisciplinary collaborations to develop holistic AD intervention strategies.

Disclosures

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