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Review Article

The Preventive and Therapeutic Prospects of Physical Activity on Alzheimer's Disease and the Potential Underlying Mechanisms

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Abstract

Alzheimer's disease, the most prevalent form of dementia, is a fatal neurodegenerative disorder. The risk factors of Alzheimer's disease include age, genetics, lifestyle, health conditions and other external stressors. The Coronavirus disease 2019 (COVID-19) pandemic has brought along many changes and accelerated the already significant increase in cases of Alzheimer's disease. However, Alzheimer's disease lacks a viable cure, and the existing treatment options, such as drugs, suffer from limited accessibility and numerous constraints. As a result, non-pharmacological and easily accessible interventions, such as physical activity, have garnered interest. In this review, we summarized the effect of physical activity for dementia prevention, the outcomes of different types of physical activity for Alzheimer's disease treatment, and the underlying mechanisms of physical activity. Though physical activity is a promising option for the treatment of Alzheimer's disease, due to limited results concerning long term benefits, the combination of physical activity with other non-pharmacological interventions such as music therapy, cognitive training, should also be considered.

Keywords: Physical activity; Alzheimer's disease; Aerobic exercise; Resistance exercise; Combined therapy; Cognitive health

Abbreviations

AD: Alzheimer's disease; AI: Artificial Intelligence: APOE: *Apolipoprotein E*; BDNF: Brain-Derived Neurotrophic Factor; COVID-19: Coronavirus Disease 2019; EEG: Electroencephalogram; FNDC5: Fibronectin Type III Domain-Containing Protein 5; IGF-1: Insulin-Like Growth Factor 1; MCI: Mild Cognitive Impairment; MRI: Magnetic Resonance Imaging; PINK1: PTEN-Induced Putative Kinase 1; ROS: Reactive Oxygen Species; VEGF: Vascular Endothelial Growth Factor

Introduction

Alzheimer's disease (AD), a fatal, progressive, neurodegenerative disease characterized by cognitive decline and memory loss, is the most common type of dementia. As ongoing AD cases are rising, the treatment and prevention of AD is an area of great concern and study. It is a chronic disease that is believed to develop because of multiple factors, age, genetics and family history being thought to be the greatest risk factors [1]. The percentage of AD increases greatly with age, from 5.0% for people ages 65 to 74, to 33.2% for people age 85 or older [1]. The e4 form of the *Apolipoprotein E* (APOE) gene has been found to increase the risk of an individual developing AD [1]. Family history can also be another risk factor for AD [1]. Some risk factors are modifiable, such as physical inactivity, smoking, diabetes, abdominal obesity, high cholesterol, high blood pressure and diet [1]. It is believed that modifying those risk factors can potentially prevent or delay the onset of AD cases, as well as slow down the progression of the disease [2].

Since AD is marked by symptoms of behavioral changes and structural changes such as β-amyloid and neurofibrillary tangles [3], current treatments mostly aim at alleviating symptoms such as depression, and reducing β-amyloid and tangles [1]. The pharmacological treatments of AD have shown only limited success, of either symptomatic treatment of AD that temporarily alleviates AD symptoms without addressing the underlying causes, or therapies targeting the underlying biology of AD but only with mild improvement [1].

As studies have demonstrated that metabolic abnormalities, such as insulin resistance, chronic inflammation, hyperhomocysteinemia, dyslipidemia, hypertension and hormonal deficiencies, are factors in AD progression, lifestyle changes such as physical activity could potentially prevent, slow, or reverse AD progression [4]. Studies have demonstrated that physical activity can reduce the risk of cognitive decline, indicating its potential benefit of delaying the onset of AD [5-7]. Additionally, it is found that the intervention of physical activity is beneficial on brain health regardless when it is initiated [5]. Physical activity has been noted to have positive effects not only on the aging process of the brain, but also on the progression of neurodegeneration [5]. Exercise has been shown to improve neurotransmitter release, boost blood circulation in the brain, thus activate the brain vascularization, plasticity, neurogenesis, stimulate the production of antioxidant molecules, and reduce inflammation by decreasing β-amyloid production [8]. It can enhance attention, executive function, and information processing speed [9]. Physical activity stimulates the release of endorphins, which are natural mood-boosting chemicals, which helps reduce agitation, aggression, depression, anxiety, improve mood and other behavioral symptoms commonly associated with AD [10]. Regular exercise can improve

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cardiovascular fitness, increase muscle strength and flexibility, and promote better balance and coordination. Engaging in physical activity can also help maintain a healthy weight, reduce the risk of chronic conditions such as heart disease and diabetes, and improve overall quality of life. Participating in exercise programs or group activities provides opportunities for social interaction, which can help combat feelings of isolation and loneliness often experienced by individuals with AD. Social engagement through exercise can improve mood, enhance cognitive stimulation, and foster a sense of belonging. In this review, we explore the underlying mechanisms of physical activity on AD, and the effects of different types of physical activity on AD prevention or progression.

Physical Activity for AD Prevention

Regular physical exercise is proven to reduce the incidence of cardiovascular risk factors, such as diabetes, hypertension and obesity [11]. It is also reported that physical activity shows beneficial effects on brain health [5]. Therefore, physical activity has been proposed as a lifestyle intervention to reduce the incidence of AD, with epidemiological and large-scale trials carried out showing promising results [11-13].

In their analysis of the impact of seven adjustable risk factors for AD, Barnes and Yaffe discovered that physical inactivity accounted for the largest proportion of AD cases in the United States and the third largest globally [11]. According to their study, approximately 13% of AD cases worldwide, amounting to nearly 4.3 million cases, can be attributed to physical inactivity. In the United States alone, physical inactivity was linked to 21% of AD cases, surpassing 1.1 million cases. The study further estimated that a 10% reduction in the prevalence of physical inactivity could potentially prevent over 380,000 AD cases globally, with nearly 90,000 cases averted in the United States. Moreover, a more significant reduction of 25% in the prevalence of physical inactivity might prevent nearly 1 million AD cases worldwide, including 230,000 cases in the United States. Similar studies estimated the demographic risk of global AD and demonstrated the relation of low physical activity to increased risk of poor health outcomes including AD [12]. The link between total daily physical activity and the incident AD and cognitive decline was also confirmed by a study with 716 non-dementia elderly over a follow-up of 4-year course [13]. The findings indicated that individuals with low total daily physical activity had a risk of developing AD that was more than twice as high compared to those with high total daily physical activity.

Several large-scale, long-term follow-up studies revealed that higher levels of physical activity were linked to a decreased incidence of both all-cause dementia and AD [6,7,14,15]. According to the systematic review by Hamer and Chida, there is a significant inverse association between physical activity and the risk of dementia [15]. Engaging in physical activity can reduce the risk of dementia and AD by 28% and 45%.

Chang et al. conducted a study aimed at examining the impact of acute exercise on reducing the risk of AD [16]. The researchers recruited late middle-age adults who carried the *APOE4* gene, which is associated with an increased risk of developing AD. The study focused on assessing the participants' executive function following a session of acute aerobic exercise. The results revealed that the participants in the exercise groups exhibited enhanced cognitive performance after the acute exercise session. These findings suggest that exercise has the potential to serve as an intervention for reducing the risk of AD, particularly in individuals carrying the *APOE4* gene.

Physical Activity as Treatment for AD

Physical activity has been recognized as a valuable non-pharmacological intervention for individuals with AD. Here we review how different types of physical activity can be used as a treatment for AD patients and their beneficial effects (Table 1).

The effects of aerobic exercise on AD

Aerobic exercise can improve aerobic fitness, reduce the risk of chronic disease in older adults, and increase life expectancy. The vascular effects of endurance exercise are critically important for long-term cognitive health; this is possibly key in the life-style intervention for AD treatment.

The effects of aerobic exercise on brain morphology: Studies demonstrated that aerobic exercise is effective in improving decay in prefrontal and lateral temporal regions [17,18] and reducing brain atrophy in AD [19]. Fifty-nine elderly healthy volunteers aged 60 to 79 years were examined by both Magnetic Resonance Imaging (MRI) and maximal oxygen uptake (VO2) after exercise interventions [17]. For the participants in the aerobic fitness group, there was a significant increase in brain volume, in both gray and white matter regions, while no change observed in the stretching and toning group, suggesting the sparing of brain tissue in aging humans by aerobic exercise. Erickson investigated the relationship between aerobic exercise and hippocampal volume in elderly people [18]. The analysis of MRI results in 165 nondemented older adults after exercise intervention found that higher levels of aerobic fitness are associated with increased hippocampal volume and better spatial memory. The benefit of aerobic exercise was confirmed by the study in early AD patients, where MRI and VO2 were monitored after early-stage AD patients (n=57) received cardiorespiratory fitness and compared with the nondemented controlled group (n=64) [19]. The results revealed a relationship between higher fitness level in early AD patients and preserved brain volume.

A randomized controlled trial by Morris et al. also reported brain volume change after comparing the effects of aerobic exercise with those of non-aerobic exercises (core strengthening, resistance bands, modified tai chi, modified yoga) on early AD patients (n=76) over the course of 6 months [20]. Their MRI results presented evidence of brain volume change as a result of aerobic exercise.

The effects of aerobic exercise on cognition: The strong evidence of aerobic exercise as a disease-modifying treatment for AD lies primarily in the studies in animal models, while its effects on cognition in human studies are inconsistent, some showing no effects [21,22], some showing moderate effects [23-25].

To evaluate the effectiveness of exercise intervention, Angiolillo et al. compared the effects of aerobic exercise training with other non-pharmacological treatments on cognitive functions of mild/moderate AD patients (N=30) [9]. The experimental group (N=15) received aerobic exercise training, while the control group (N=15) received reality orientation therapy, music therapy, motor, proprioceptive and postural rehabilitation. Their results show that aerobic exercise has potential to improve cognitive functions such as verbal episodic memory, visual-spatial reasoning abilities, processing speed and selective attention in AD patients. Hoffmann et al. conducted a randomized controlled trial to assess the effects of a moderate-to-high intensity aerobic exercise program in patients with mild AD [10]. A total of 200 participants were randomly grouped into intervention group

Table 1: Benefits and limitations of different types of physical activities.

Type	Purpose	Benefits	Limitations
Aerobic exercise • Running • Jogging • Cycling • Swimming • Dancing	Fitness that increases heart rate and breathing, promote cardiovascular activities	Cardiovascular health Weight management Cognitive benefits Mood enhancement Variety of options	High impact Potential of overuse injuries Time and accessibility Monotony
Resistance exercise • Free weights • Weight machines • Resistance bands • Push-ups • Squats	Working against a force to strengthen and tone muscles	Strength and muscle tone Bone health Metabolic benefits Joint stability Body composition benefits Flexibility and balance	Learning curve and technique Muscle soreness Equipment or gym access Progression challenges Potential for injury
Flexibility and stretching exercise • Static stretching • Yoga • Pilates	Exercises focus on improving joint range of motion and stretching muscles	Joint range of motion Muscle tension- Injury prevention Posture Stress relief	Overstretching risks Individual variation Time commitment Lack of cardiovascular benefits
Balance and stability exercise • Tai Chi • Balance boards • Stability balls	Exercises focus on improving coordination, stability and proprioception	Fall prevention Functional performance Core strength and stability Joint stability	Potential for overexertion Initial difficulty Equipment or space requirements Individual variations
Group exercise classes • Zumba • Kickboxing • Spinning	Structured exercise classes led by an instructor	Motivation Accountability Social interaction Variety and structure Expert guidance Fun and energizing	Lack of individual attention Limited flexibility in schedule Limited flexibility in format Crowded or limited space Inconsistency in instructors

and control group. The intervention group received three exercise sessions of moderate-to-high intensity of aerobic training every week with the duration of 16 weeks. The results of the intervention showed that there had been significant improvement on neuropsychiatric symptoms, but no benefits on cognitive performance.

The majority of studies have demonstrated that exercise can improve physical and cognitive outcomes in relatively short duration (<1 year). Cox et al. assessed adherence of physical exercise intervention in participants 60 years and older with Mild Cognitive Impairment (MCI) or subjective memory complaints (n=106) [26]. All the participants wore a pedometer to record their usual physical activities. The intervention group received a 24-month home-based program of to achieve a moderate level of aerobic exercise, while the control group was told to keep their usual physical activities. The study confirmed that long-term physical activity adherence is achievable and acceptable. The participants in the exercise intervention group achieved an improved overall health profile, with long-term improvement in leg strength, lower fat mass and hip circumference, and short-term improvement in body mass.

To understand the inconsistency of the available studies and delve deeper into the investigation of the effect of aerobic exercise on AD patients, Yu et al. conducted a study of an aerobic exercise intervention with the duration of 6 months to mild-to-moderate AD patients (n=78), comparing aerobic fitness and cognitive performance for the intervention group (cycling) and the control group (stretching) [27]. The results confirmed the inter-individual differences in aerobic fitness and cognitive responses to aerobic exercise, which underlines the inconsistent cognitive benefits in previous studies.

A meta-analysis of aerobic exercise effect on AD patients included 12 randomized controlled trials and 795 samples and concluded that aerobic exercise can effectively improve intellectual and cognitive impairment in AD patients [28]. The study also compared different aerobic exercise modes and found that spinning aerobic exercise has greater therapeutic effect on AD patients compared to fit aerobics.

The effects of resistance training on AD

For elderly with AD, loss of muscle strength is a common symptom. Resistance training reduces bone loss, maintains muscle, increases balance, and decreases the risk of falling. Apart from the general positive effects of physical activity on neuropsychiatric symptoms of AD patients, muscle contraction helps blood circulation up to the brain, is corelated with better cognitive function [5].

The effects of resistance training on cognition in AD patients: Research has shown that lower limb muscles, higher leg strength in particular, are correlated with better cognitive function [29]. Recently, Broadhouse et al. evaluated the long-term neurostructural and cognitive impact of resistance exercise on AD patients with MCI (n=100) over the course of 18-month trial [30]. The participants were randomly assigned to four training groups to receive different combination of resistance training and cognitive training with six month of treatment duration, followed by a 12-month post-intervention assessment course. Resistance exercise was found to achieve better global cognitive and executive function and the intervention slowed the degeneration process of AD-vulnerable hippocampal subfields for at least 12 months post-intervention, demonstrating the longitude effect of resistance training.

A randomized, controlled trial conducted by Mavros et al. assessed the improvement in cognitive function after resistance training for older adults with MCI (N=100) and found significant improvement in muscle strength, aerobic capacity and enhancement in cognitive function after high intensity resistance training [31]. The study not only provided evidence for resistance training as a suitable intervention for AD, but also established the correlation between muscle strength, aerobic capacity and cognitive function improvement.

The effects of resistance training on neuropsychiatric behaviors in AD patients

To further evaluate the effects of resistance exercise on elderly patients with MCI, Hong et al. measured the Electroencephalogram (EEG) patterns on MCI patients (N=22) compared with healthy participants (N=25) [32]. The 12-week resistance exercise program shows positive effects on both EEG measurements and the neuropsychological tests. Resistance exercise is also found to be effective on the depression and activities of daily living in people with mild dementia in a day care center setting (N=30) [33].

To compare the effects of different modes of exercise, aerobic and resistance, Tsai et al. monitored molecular markers to evaluate exercise-induced neuropsychiatric changes on older adults with MCI (N=66). Both exercise modes are found to improve behavioral performances and enhance the circulation of neuroprotective growth factors [34].

Group exercise improves social engagement in AD patients

Group exercise helps with maintaining social connections and improving physical well-being; it is believed that engaging in group exercise on a daily basis can improve both physiological and psychological processes, and in turn, enhance the cognitive abilities of individuals with AD.

To evaluate the feasibility of low-cost, group-based exercise approach to enhance the cognitive function on AD patients, Shaw et al. carried out a study on participants with mild to moderate AD (N=40) [35]. After receiving eight weeks of group exercise composed of different modes of exercise, including balance, resistance, aerobic and flexibility exercises, the intervention group showed significant improvement in cognitive functions and performed much better in activities of daily living. Similar study was performed by Vreugdenhil et al. to analyze the effectiveness of a community-based exercise program on community-dwelling AD patients (N=40), and confirmed that such community-based exercise program can improve both physical and cognitive functions, as well as promote the independence in activities of daily living in AD patients [36].

The potential benefits of multimodal intervention for AD treatment

Various forms of physical activity have already demonstrated benefits for individuals. To optimize the impact of these exercises, there is a growing inclination to explore the effects of multimodal protocols. As explained by Saunders et al., multimodal protocols encompass interventions that combine different components of exercises, including balance, endurance, resistance, and flexibility exercises [37].

The positive effects of multimodal physical exercise program on institutionalized elderly were confirmed by the measurements of functional outcomes, cognitive performance, quality of life, epigenetic markers and BDNF levels, where in the study, a multimodal exercise protocol was introduced to participants without dementia (N=8) over an 8-week course and found to promote significant improvement in cognitive functions and quality of life [38]. The dose and duration of the exercise was studied by Kaushal et al. [39]. Elderly participants without dementia (N=110) were allocated to three groups to either receive higher-dose and lower-dose multimodal exercise, or no treatment for a duration of 12 weeks. The results found positive correlation between exercise duration, dosage and improvement in daily activities for elderly individuals. Such effects were also evaluated for AD patients, where the study of a 12-week multimodal physical exercise program on elderly people with either MCI or AD (N=28) proved the improvement in the mobility and executive function for participants with MCI, but not for participants with AD, suggesting its effectiveness in the early stages of neurocognitive disorder [40].

When Ayari conducted a systematic review to explore in exercise details, such as type, frequency, duration, intensity, and volume for both human and animal models with MCI or dementia, multimodal training stands out to be the most effective approach to reduce pro-inflammatory cytokines and enhance anti-inflammatory cytokines for both MCI and AD [41]. Multimodal exercise was also compared with exercises of single mode in a study over a large sample size of AD patients (N=811) [42]. The results indicated higher improvement in activities of daily living for the group receiving multimodal exercise training.

Combined Therapy to Address Diverse Risk Factors Associated with AD

The utilization of combined therapy for AD treatment is increasingly gaining popularity. Combined therapy for non-pharmacological AD treatment refers to an approach that integrates multiple interventions or strategies to target various aspects of the disease and its symptoms. By incorporating a range of non-pharmacological interventions, such as cognitive training, physical activity, music therapy, art therapy, and reminiscence therapy, combined therapy can target multiple areas simultaneously. Such comprehensive approach addresses the complex nature of the disease and provides a more holistic treatment strategy. In addition, by considering the unique needs, preferences, and abilities of each individual, a combination of interventions can be selected and adjusted over time to optimize the treatment outcomes. This individualized approach recognizes the heterogeneity of the disease and the importance of adapting the treatment to suit each person's specific circumstances. Combined therapy for non-pharmacological AD treatment offers a multidimensional, synergistic, and individualized approach to address the diverse challenges associated with the disease.

Among the various lifestyle factors, nutrition and physical activity have gained significant attention due to their potential role in the prevention and management of this complex disease. Rege et al. explore the positive effects of physical activity and proper nutrition in reducing the risk of developing AD [43]. They reviewed 164 references, including epidemiological, longitudinal, cross-sectional, intervention, and randomized controlled studies. It emphasizes the impact of various dietary supplements and physical exercise on cognitive function in both humans and animal models with AD and MCI. The findings underscore the therapeutic potential of a combination of balanced diet and physical activity in reducing the risk of AD.

Rao et al. reviewed multi-therapeutic strategies that identify and mitigate specific risk factors for each affected individual [44]. The article systematically examines studies that have incorporated multiple strategies to simultaneously target various factors in order to reverse or treat cognitive decline. The findings from these research studies emphasize the need for a multifactorial approach to address the diverse risk factors associated with AD. While a single-drug approach may delay memory loss to some extent, it has not yet proven effective in preventing or reversing the disease. Factors such as diet, physical activity, sleep, stress, and environment all contribute to the

progression of AD, underscoring the importance of a comprehensive optimization of network support and function as a rational therapeutic strategy. Therefore, a multi-therapeutic program that concurrently targets multiple factors within the AD network may offer greater efficacy compared to a mono-therapeutic approach.

To understand lifestyle-related risk factors and the outcomes of innovative trials focused on preventing cognitive decline and dementia, three significant multidomain trials were review and all led to the findings that directing preventive interventions towards individuals at risk is an effective strategy [45]. Another review encompassed 28 studies involving a total of 2,711 older adults diagnosed with MCI, to investigate whether multidomain interventions lead to more substantial enhancements in cognition among older adults with MCI compared to single interventions [46]. The findings of this review indicate that short-term multidomain interventions lasting less than one year were associated with improvements in global cognition, executive function, memory, and verbal fluency in comparison to single interventions for older adults with MCI.

Underlying Mechanisms of Physical Activity on AD

Physical activity has been shown to have a positive impact on brain plasticity and neurogenesis, which are crucial processes for maintaining and enhancing brain function. Physical activity causes increased blood flow to the brain, which triggers biochemical changes that enhance the brain connectivity, improve the integrity of white matter, promote the growth of brain cells, produce brain growth factors, maintain vascular health, alleviate oxidative stress and reduce neuroinflammation (Figure 1). There are growing number of studies suggesting that aerobic exercise can promote neuroplasticity [47,48], induce increased hippocampal neurogenesis, and protect against or reverse age-related hippocampal atrophy [49]. Regular exercise improves cerebrovascular and endothelial function, reduces oxidative stress and systemic inflammation, and helps regulate immune function, which may contribute to improved neuronal function [50,51]. Brain plasticity depends on the ability of neurons to modify the strength and composition of their connections in response to both external and internal stimuli [52]. The long-term potentiation in synaptic efficacy is the most widely proposed mechanism of learning and memory [52]. Impaired synaptic function leads to a decline in memory processing, contributing to neurological and cognitive disorders [52].

Physical activity improves brain plasticity and neurogenesis

Physical activity stimulates the production and release of neurotrophic factors, such as BDNF, IGF-1, and VEGF. These factors play a vital role in promoting neuronal survival, growth, and differentiation, as well as in regulating synaptic plasticity. By increasing the levels of neurotrophic factors, physical activity supports the survival of existing neurons and facilitates the generation of new neurons. Physical activity also increases cerebral blood flow, leading to improved oxygen and nutrient delivery to the brain. This increased blood flow helps in the removal of metabolic waste products and supports the growth and function of brain cells. Adequate blood supply is essential for maintaining the health of neurons and supporting neuroplasticity processes. The hippocampus, a region of the brain critical for learning and memory, is particularly responsive to physical activity. Positive effects of hippocampal volume increase and synaptic connections enhancement with relation to physical

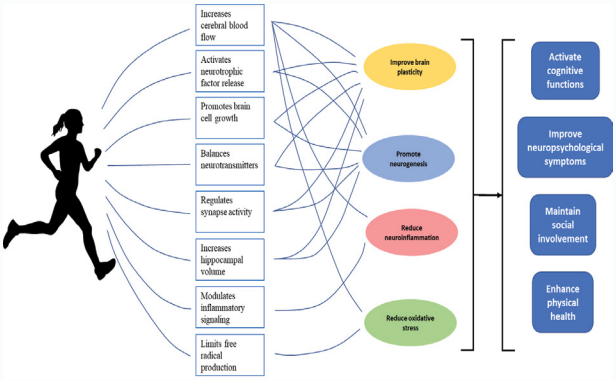

Figure 1: Effects of exercise on AD: from underlying mechanisms to benefits. Through various physiological pathways, exercise can improve brain plasticity and neurogenesis; reduce neuroinflammation and oxidative stress, resulting in positive effects on cognition, neuropsychological behaviors, social engagement as well as physical health.

activity have been found [17-19]. These structural changes in the hippocampus are associated with improvements in learning, memory, and cognitive function [17]. Physical activity influences the release and balance of various neurotransmitters in the brain, including serotonin, dopamine, and norepinephrine [50]. These neurotransmitters play a role in regulating mood, motivation, and cognition. By modulating neurotransmitter levels, physical activity can enhance mood, reduce stress, and improve cognitive function [50]. Physical activity has been found to enhance functional connectivity between different brain regions [53]. It strengthens the communication and coordination between neural networks, which is essential for efficient cognitive processing [53]. Improved brain connectivity allows for more efficient information processing, leading to enhanced cognitive abilities [53]. Morris et al characterized the blood biomarker response to acute exercise in 80 individuals, including 62 older adults and 18 young controls [54]. Their study used BDNF, VEGF, IGF-1 and Lactate as biomarkers to monitor their changes after moderate intensity exercise. The results show a significant increase in circulating BDNF and lactate after aerobic exercise for both elderly group and young group, suggesting that aerobic exercise may be beneficial to brain health and reduce the risk of cognitive decline.

The brain's ability to sense physical activity implies that peripheral factors induced by muscles facilitate direct communication between muscle and brain functions [5]. Among the factors that regulate hippocampal function, myokines released by muscles play an important role. There is a growing body of evidence indicating that the myokine cathepsin B has the ability to cross the blood-brain barrier [5]. Its presence in the brain promotes the production of BDNF, which in turn enhances neurogenesis, memory formation, and learning abilities. The signaling of myokines, along with other factors released by muscles, as well as exercise-induced hepatokines and adipokines, are believed to play a role in mediating the positive effects of exercise on neurogenesis, cognitive function, appetite, and metabolism [55]. This suggests the presence of a muscle-brain endocrine loop that facilitates communication between the two organs [55]. Since AD has been linked to impaired hormonal signaling within the brain, Lourenco et al. demonstrate that the levels of FNDC5/irisin, a myokine released during exercise through cleavage of the membrane-bound precursor protein FNDC5, are diminished in both the hippocampi and cerebrospinal fluid of individuals with AD, as well

as in experimental AD mouse models [56]. The finding highlighted the significance of FNDC5/irisin as a novel mediator that counteracts synapse failure and memory impairment in AD mice, emphasizing its role in facilitating the beneficial effects of physical activity.

Researchers examined the impact of long-term physical and cognitive activation on neurogenesis, focusing specifically on the loss of hippocampal neurons and the resulting behavioral impairments in the AD mice, which exhibit overexpression of Aβ4-42, one of the most abundant β-amyloid species, without any mutations, experience age-related hippocampal neuron loss accompanied by significant memory decline [57]. From notable alterations in the gene expression profile of AD mice, the findings reveal that extended periods of exercise effectively reduce neuron loss and fully restore spatial memory deficits. The compelling evidence heightened physical activity mitigates both neuron loss and behavioral deficits in a transgenic mouse model of AD.

Physical activity reduces oxidative stress and inflammation in the brain

Regular physical activity has been shown to reduce oxidative stress and inflammation in the brain [58-60]. Oxidative stress and inflammation are associated with neurodegenerative processes and can impair neuronal function and plasticity. By mitigating these harmful processes, physical activity creates an environment conducive to neuroplasticity and neurogenesis.

Inflammation in AD has emerged as a central pathology that likely plays a role in onset and progression of the disease. Kinney et al. suggested neuroinflammation as the underlying mechanism for AD and provided an overview of the interactions of inflammatory signaling and the progression of AD [59]. They also discussed a number of possible mechanisms that may account for connections between altered inflammatory signaling and the changes observed in AD. According to the review, it is indicated that persistent inflammation in the brain accelerates other core pathologies: the presence of β-amyloid plaques and neurofibrillary tangles. This implies that targeting inflammatory mechanisms can also be a promising avenue for therapeutic development.

It has been observed that neuroinflammation in AD is characterized by persistent activation of pro-inflammatory microglia and NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) inflammasomes [58]. Continuous activation of microglia by damaged signals originating from both the brain and peripheral tissues leads to a constant inflammatory response. Furthermore, the chronic inflammatory state exacerbates endoplasmic reticulum oxidative stress in microglia, triggering immune responses that contribute to the development and progression of AD. It has been concluded that physical activity modulates the immune response in the central nervous system, thus reduce the risk of neuroinflammation [58].

Researchers conducted a study to investigate the potential pathways affected by physical activity in the cortex area of individuals with AD by running various gene analysis on isolated cerebral cortex samples obtained from eight AD mice (12 weeks old) [61]. The analysis revealed that there were 412 significantly differentially expressed genes in the exercise group compared to the control group. Among the top 10 upregulated genes in the exercise group, most were associated with neuroinflammation, while the top 10 downregulated genes had connections to vascularization, membrane transport, learning memory, and chemokine signaling.

It is now well-established that impaired insulin signaling, a characteristic feature of diabetes, plays a significant role in the development of AD [62]. The review by Felice et al. explored the evidence demonstrating that brain inflammation and the stimulation of cellular stress response mechanisms contribute to the disruption of brain insulin signaling in AD, thus linking impaired insulin signaling with AD pathology. The relationship between insulin signaling dysfunction and chronic stresses creates a favorable environment for medical conditions that increase the risk of AD, including diabetes, obesity, depression, and cardiovascular and cerebrovascular diseases.

Kinney et al. present a comprehensive examination of the role of inflammation in AD, with a specific focus on the involvement of microglia, the brain's resident macrophages, and other immune cells [59]. The sustained activation of these immune cells has been found to contribute to the progression of amyloid and tau pathology, establishing a potential link in the development of the disorder.

Oxidative stress causes dysfunction of neuronal mitochondria, the oxidation of macromolecules, the generation of Reactive Oxygen Species (ROS) by the binding of metal ions to β-amyloid plaques and the upregulation of tau and β-amyloid synthesis, resulting in dementia including AD [60]. In their study, Zhao et al. identified the significant involvement of the abnormally activated PINK1 (PTEN-induced putative kinase 1)/Parkin pathway-mediated mitophagy in the progression and pathogenesis of AD in 6-month-old AD mice. The study utilized the lysosomal inhibitor chloroquine to demonstrate the positive effects of a 12-week treadmill exercise program on mitochondrial function, β-amyloid plaque accumulation, and cognitive decline in AD mice. More interestingly, it was found that treadmill exercise restored PINK1/Parkin-mediated mitophagy in the hippocampus of AD mice, highlighting the potential of activating PINK1/Parkin-mediated mitophagy as a promising therapeutic approach for treating AD.

Conclusions and Perspectives

Exercise can be beneficial for individuals with AD, but it also has certain limitations as a non-pharmacological treatment. As AD progresses, individuals may experience physical and cognitive decline, making it challenging to engage in exercise activities persistently and safely.

However, despite the limitation mentioned above, exercise can still have positive effects on the overall well-being of individuals with AD. Exercise has been associated with improved cognitive function, improved mood and reduced symptoms of depression and anxiety in individuals with AD. In this review, we discussed about the benefits that combined therapy can bring. While exercise alone cannot cure or reverse AD effectively, emerging research suggests that it may have disease-modifying effects. Combining exercise with other non-pharmacological or pharmacological interventions, such as music therapy, art therapy, aromatherapy, cognitive stimulation, nutritional management, sleep management, or animal-assisted therapy, can provide a holistic approach to AD management that addresses cognitive, physical, social, emotional, and environmental aspects of the disease. Such comprehensive approach can help improve overall functioning, maintain independence, enhance well-being, and potentially slow down disease progression.

Studies have shown that the response to exercise can vary among individuals with AD. While some individuals may experience cognitive and physical benefits from exercise, others may not show

significant improvement. The effectiveness of exercise as a non-pharmacological treatment can depend on factors such as the stage of the disease, overall health, and individual variability. Therefore, it is essential to adapt exercise programs to the individual's abilities and consult with healthcare professionals to ensure safety and appropriateness. In addition, technology can be implemented to track AD patients' progress with current treatment, to personalize patients' treatment plans, and to help alleviate AD symptoms. As technology increasingly improves and becomes more integrated within medicine, AD patient treatment plans can be monitored and created using technology such as artificial intelligence (AI). By incorporating AI within a patient's treatment, the progression of AD within a patient can be better observed, and a personalized effectual treatment plan and methods can be assigned to a patient.

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