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Beneficial Effects of Exercise on Brain-Derived Neurotrophic Factor in Subjects with Alzheimer; a Systematic Review

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ABSTRACT

Aims There are treatments that seem to help maintain mental skills and reduce the effects of Alzheimer's disease. On the other hand, physical exercises can have a protective effect against deterioration. The level of BDNF decreases in AD, and the decrease in this factor is consistent with the decrease in hippocampal volume in this disease. This study aimed to evaluate the effects of exercises on Brain-Derived Neurotrophic Factor levels in patients with Alzheimer's.
Information & Methods This study was conducted based on the PRISMA guidelines in 2023. English papers on the effects of exercises on BDNF levels in subjects with Alzheimer's were included. Unpublished papers, review papers, and studies with deficient information were not included. Keywords were searched in PubMed, Scopus, EuropePMC, Cochrane Central Database, Embase, and Web of Science databases. All the studies were managed with Endnote™ X9.2 software.
Findings Twelve papers were reviewed, comprising 4 human and 8 animal studies. The periods for human studies lasted 26 to 52 weeks. Animal studies lasted 4 to 13 weeks. The samples were collected from plasma in human studies, while most animal studies were conducted on the expression of BDNF in the hippocampus (n=6). Out of 12 papers, 3 human papers and 8 animal studies showed that exercises significantly increased the concentration of the expression of BDNF
Conclusion Exercise positively improves and increases the expression and concentrations of Brain-Derived Neurotrophic Factor.

Keywords Alzheimer; Brain-Derived Neurotrophic Factor; Exercise

CITATION LINKS

[1] Alzheimer's disease: Causes ... [2] Detection of Alzheimer's disease ... [3] Mitochondria and calcium in Alzheimer's ... [4] Diffusion tensor imaging reveals greater ... [5] Diagnosis and treatment methods in ... [6] Clinical approach to ... [7] Neuropsychological assessment in patients ... [8] Evaluating the distinction between ... [9] Neuropsychological assessment of driving ... [10] Alzheimer's disease and other dementias, ... [11] Gut-brain axis in Alzheimer's disease: ... [12] The role of brain-derived neurotrophic ... [13] Neurotrophins in the neuropathophysiology, ... [14] The BDNF Val66Met SNP modulates ... [15] Evaluation of hippocampal volume ... [16] Brain-derived neurotrophic factor in ... [17] Targeting Akt/CREB/BDNF signaling ... [18] Microglia and immunotherapy in ... [19] Consequences of physical inactivity ... [20] The effect of physical exercise on cognitive ... [21] Physical exercise during exposure to 40-Hz ... [22] Exercise intensity and recovery on circulating ... [23] Physical exercise neuroprotects ... [24] Combined adult neurogenesis and BDNF ... [25] Research methods & reporting-preferred ... [26] Research synthesis and meta-analysis: ... [27] Acute aerobic exercise increases ... [28] ffects of aerobic exercise training ... [29] Physical exercise in MCI elderly ... [30] BDNF responses in healthy older ... [31] Neuroprotective effects of treadmill ... [32] Treadmill exercise sex-dependently ... [33] Protective effects of different exercise ... [34] Treadmill exercise prevents learning ... [35] Treadmill exercise alleviates impairment of ... [36] Exercise decreases BACE and APP levels ... [37] Treadmill exercise improves short-term ... [38] Running exercise delays neurodegeneration ... [39] 2015 Alzheimer's disease facts ... [40] 2017 Alzheimer's disease ... [41] Dementia associated with seizure ... [42] The relationship between frailty, functional ... [43] Oxidative DNA damage in mild cognitive ... [44] Oxidative stress and vascular ... [45] The effects of oxidative stress on female ... [46] Cyclooxygenase and inflammation in ... [47] α-lipoic acid improves abnormal behavior by ... [48] Effects of exercise training on the autonomic ... [49] Impact of fermentation conditions ... [50] Recent advances on the anti-inflammatory ...

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Introduction

Alzheimer's disease (AD) is a type of brain dysfunction that gradually degrades the patient's mental abilities [1]. It is normal for people to become a little forgetful as they age, but memory disorder progresses gradually in AD [2]. Alzheimer's causes the death of nerve cells and loss of tissue throughout the brain [3]. With the severity of the disease, the brain tissue shrinks, and the areas containing cerebrospinal fluid become larger [4].

The damage caused by Alzheimer's affects the affected person's memory, speech, and perception. Memory problems are usually one of the first symptoms of Alzheimer's [5]. However, the initial symptoms of this disease vary from person to person. Complications such as impaired performance in other aspects of thinking, such as finding the right words while speaking, visual/spatial problems, and impaired reasoning or judgment can be another sign of the early stages of AD [6, 7]. Memory problems are usually one of the first symptoms of Alzheimer's [8]. However, the initial symptoms of this disease vary from person to person. Complications such as impaired performance in other aspects of thinking, such as finding the right words while speaking, visual/spatial problems, and impaired reasoning or judgment can be another sign of the early stages of Alzheimer's disease [9, 10].

Alzheimer's disease affects the secretion of many neurotrophins [11]. These are nerve growth factors and are a type of cytokine. Neurotrophins, including Brain-Derived Neurotrophic Factor (BDNF), are key in increasing sympathetic activity and blood pressure [12, 13]. Studies have shown that the level of BDNF decreases in AD, and the decrease in this factor is consistent with the decrease in hippocampal volume in this disease [14, 15]. BDNF affects the intracellular signaling pathway of the proliferation of hippocampus cells and thus interferes in the development of AD [16, 17].

Alzheimer's has no cure, and there is no way to slow down the rate of nerve damage that it causes in the brain [18]. However, some treatments seem to help maintain mental skills and reduce the effects of the disease. On the other hand, physical exercises can protect against deterioration [19]. Increasing physical activity is effective in different lifestyles and increases brain activity, especially in the hippocampus area (memory center and learning), thus decreasing AD's secondary effects [20, 21]. It seems that the aerobic exercise program can effectively improve the neuropsychological functions of these patients. Several studies have reported the efficiency of exercises on BDNF in AD [22-24], but there is no comprehensive review on the effects of exercise on BDNF in AD. Thus, this study aimed to evaluate the effects of exercises on Brain-Derived Neurotrophic Factor levels in patients with Alzheimer's.

Information and Methods

This study was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [25] in 2023. English papers on the effects of exercises on BDNF levels in subjects with Alzheimer's were included.

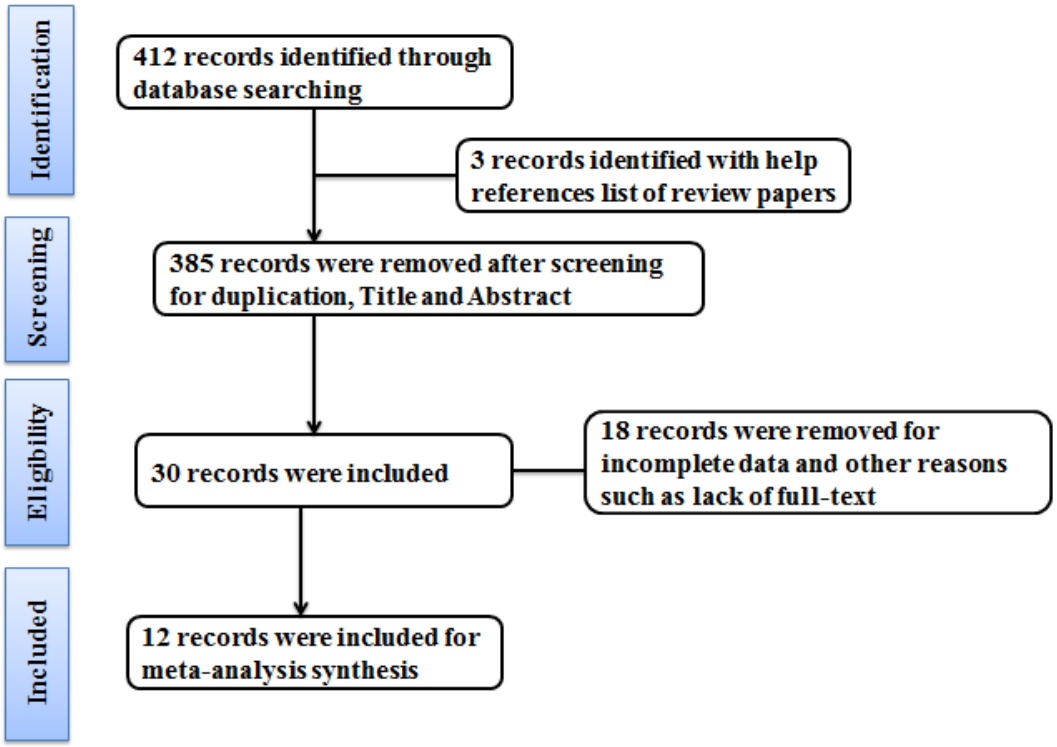

Figure 1. PRISMA flow diagram for included studies for the effects of exercises on BDNF

Studies lacking complete data (e.g., lack of subjects, their numbers, periods, sample collection, and unclear results) were excluded. Unpublished papers, review papers, and studies with deficient information were not included. Papers were searched with keywords of "exercise" OR "BDNF" OR "neurotrophins" OR "rats" OR "mice" OR "humans". The second strategy was to search reference lists in review articles for related articles. Articles were searched based on title and abstract. Duplicate papers were excluded, and potential papers were included. Searches were finalized on September 5th, 2023. Searches lasted for weeks to obtain final papers. Reviews and other mentioned non-related papers were excluded.

A standardized data coding form was prepared to extract the information from each study, including authors and publication year, study sample characteristics (number of subjects and their type), period of study, and results. Each study has only participated in the current research once [26]. In the current study, 12 articles were identified with the help of a database search and searching in a reference list. Keywords were searched in PubMed, Scopus, EuropePMC, Cochrane Central Database, Embase, and Web of Science databases (Figure 1). All the studies were managed with Endnote™ X9.2 (Thomson Reuters, Philadelphia, PA, USA) software. All the papers were read and investigated by two reviewers.

Findings

Twelve papers were reviewed, comprising 4 human and 8 animal studies. The periods for human studies lasted 26 to 52 weeks. Animal studies lasted 4 to 13 weeks. The samples were collected from plasma in human studies, while most animal studies were conducted on the expression of BDNF in the hippocampus (n=6). Out of 12 papers, 3 human papers and 8 animal studies showed that exercises significantly increased the concentration of the expression of BDNF (Table 1).

Table 1. Studies conducted on the effects of exercises on BDNF in subjects

Authors	Subjects	No.	Periods	Region	Results
Coelho *et al.* [27]	Older patients	21	26 weeks	Plasma	BDNF concentration increasing
Gaitan *et al.* [28]	Middle-age	23	26 weeks	Plasma	BDNF concentration low affected
Nascimento *et al.* [29]	Older patients	17	1 year	Plasma	BDNF concentration increasing
Håkansson *et al.* [30]	Older patients	90	-	Serum	BDNF concentration increasing
Koo *et al.* [31]	Mice-24 months	8	3 months	Cortex	BDNF expression increasing
Naghibi *et al.* [32]	Rats-11-12 weeks	15	3 months	Hippocampus/Prefrontal Cortex	BDNF expression increasing
Özbeyli *et al.* [33]	Rats-6 months	64	6 weeks	Hippocampus	BDNF expression increasing
Dao *et al.* [34]	Adult Wistar rats	48	4 weeks	Temporal portion	BDNF expression increasing
Sim *et al.* [35]	Adult Sprague-Dawley rats	48	8 weeks	Hippocampus	BDNF expression increasing
Alkadhi & Dao [36]	Adult Wistar rats	48	4 weeks	Hippocampus	BDNF expression increasing
Kim *et al.* [37]	Adult Wistar rats	48	4 weeks	Hippocampus	BDNF expression increasing
Lin *et al.* [38]	Tg mice-4 months	48	10 weeks	Hippocampus	BDNF expression increasing

Discussion

This systematic review assessed the effects of exercises on BDNF levels in subjects with Alzheimer's. Most human studies were conducted on middle-aged and elderly people. It is a common disease in elderly people. Alzheimer's disease in the elderly is a brain disorder that slowly destroys memory and thinking skills and, ultimately, the ability to do the simplest tasks. Recent estimates show that Alzheimer's disease is the third leading cause of death in the elderly after heart disease and cancer [39, 40].

Alzheimer's in the elderly is the most common cause of dementia among the elderly. Dementia is the loss of cognitive function-thinking, remembering, reasoning, and behavioral abilities to the extent that it interferes with a person's daily life and activities [41]. The severity of dementia ranges from the mildest stage, when it just begins to affect a person's functioning, to the most severe stage, when the person must be completely dependent on others for basic activities of daily living [42]. The damage occurs first in the hippocampus and entorhinal cortex, parts of the brain essential to forming memories. As more nerve cells die, other brain parts are affected and diminish. In the late stage of Alzheimer's in the elderly, the damage is extensive, and the brain tissue has significantly diminished [43].

Most studies on animal models were also conducted on elderly animals. Thus, animal models emphasize aged animals. The studies had differences for periods. Human studies were conducted for longer times, 26 weeks and longer. Since human studies were scarce, a relation between the period and efficiency of exercises can be stated. However, longer and shorter animal studies reported the positive effects. It can be stated that short-term exercises can increase BDNF in animal models. The results also showed that exercises influence the concentration of BDNF in the plasma. A study showed that exercises cannot positively affect the concentration plasma of BDNF [28]. The plasma concentration is not a good criterion for assessing BDNF and may not show the BDNF changes. However, most animal studies were conducted on the expression of BDNF. The expression of genes and changes in the hippocampus prove the effects of exercises on BDNF changes. Exercise could positively affect BDNF levels in the plasma and hippocampus. The exact mechanism that shows the

effects exercises on the changes of the factor has not been determined. However, exercises may help improve this factor's concentration or its expression by increasing angiogenesis and reducing inflammation and oxidative stress [44, 45]. AD is accompanied with stress and inflammation [46, 47]. Several studies have reported anti-inflammatory and antioxidant properties of exercises [48-50].

Thus, exercises can be considered a supplementary treatment for patients with AD. We recommend clinical studies on humans with the help of assessing the expression of BDNF to elucidate the exercises on BDNF concentration.

Conclusion

Exercise has positive effects on improving and increasing the expression and concentrations of Brain-Derived Neurotrophic Factor.

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