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Impact of physical activity on the development of Alzheimer's disease.

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Abstract

Alzheimer's disease is the most common form of dementia and is a challenge for the modern world due to the due to aging populations. Researchers are trying their best to understand the mechanisms of onset and find effective ways to treat and prevent this disease. The purpose of the following paper is to present the impact of physical activity in the development of Alzheimer's disease. Numerous studies confirm that regular workouts have a positive reflection in the form of slowing the aging of the brain and alleviation of neuropsychiatric symptoms in affected individuals. During muscle work irisin is produced, which plays an important role in the formation of neurons and exhibits an anti-inflammatory effects. This review also looks at the aspect of maintaining proper composition of the gut microbiota, whose imbalance can promote the process of neuronal inflammation and cognitive dysfunction. Attention is also given to issues of training intensity and the effect of of exercise on blood flow in the brain. All of these elements play an important role in preventing and slowing down neurodegeneration.

Purpose : The purpose of this scientific paper is to review the current knowledge of the effects of physical activity on the development of Alzheimer's disease.

Review methods : We conducted our study as a literature review based on information gathered from PubMed, Embase, Google Scholar using combinations of the following keywords : Alzheimer's disease ; dementia ; physical activity ; cerebral blood flow ; gut-brain axis ; irisin.

The state of knowledge : Alzheimer's disease is the most common type of dementia and one of the main neurodegenerative disorders affecting elderly people. Numerous studies confirm that regular exercise has a positive effect on slowing down brain aging and alleviating neuropsychiatric symptoms in patients. According to current knowledge, nerve cell degeneration can be exacerbated by peripheral inflammation that occurs in obesity. An imbalance of bacterial flora in the gastrointestinal tract causes systemic inflammation in the body. This in turn leads to excessive production of pro-inflammatory cytokines and activation of microglia so that the blood-brain barrier becomes leaky. Maintaining the appropriate composition of the gut microbiota plays an important role, as its imbalance can promote neuronal inflammation and cognitive impairment. During physical activity, irisin protein is produced in muscle tissue, which plays an important role in neuronal formation and exhibits anti-inflammatory effects. Currently, there is evidence that irisin can provide a number of beneficial effects, mainly through mechanisms that positively affect the gut microbiome. Attention is also given to issues of training intensity and the effect of exercise on cerebral blood flow. All these factors play an important role in preventing and slowing down neurodegeneration.

Conclusion : Based on a review of the available literature, a significant effect of physical activity on the development of Alzheimer's disease can be demonstrated. The accumulated data suggest that physical activity is one of the main protective factors against the development and progression of Alzheimer's disease. Physical activity is associated with a reduction in cardiovascular risk factors and an increase in neuroprotective changes. The neuroprotective effect of physical exercise is dependent on its intensity. In addition, the role of the gut microbiota has been shown to be important for maintaining normal cognitive function. The protein irisin may also have significant neuroprotective potential in relation to the development and progression of cognitive disorders. Physical activity may be one of the strategies to prevent an increase in the incidence of Alzheimer's disease with positive health, economic and social implications in the future.

Keywords : Alzheimer's disease ; dementia ; physical activity ; cerebral blood flow ; gut-brain axis ; irisin

Introduction

In recent years, due to the increasing proportion of elderly people in the world's population, an increasingly dementia is becoming a greater challenge for health care. According to data from 2015 more than 46 million people worldwide suffer from the condition and studies show that by 2050 the that number will reach 131.5 million [1]. This rapid growth will have serious implications for both the economy and social functioning, and will place a serious burden on health care. As a result, the World Health Organization (WHO), realizing the implications of these changes, has identified dementia as a major public health goal, calling on governments to focus on prevention, increasingly effective treatments and improved methods of health care services [2]. The most common type of dementia is Alzheimer's disease (AD). It is also one of the main neurodegenerative disorders affecting elderly people. 24 million people worldwide suffer from AD, and it is predicted that by 2050 this number will be four times higher [3]. These dramatic statistics can be explained by the fact that the most important risk factor for this disease is age [4], and it is believed that by 2050 there will be about 1.5 billion people over the age of 65, a threefold increase over the number of such people in 2010. These frightening scenarios about the impact of Alzheimer's disease on the economy of the world as a whole, but also on the functioning of individual people with the disease, the burden on their families, caregivers, and the far too slow progress toward finding effective therapeutic methods, is causing increasing attention to be paid to prevention of the disease. One of the main methods of preventing AD is physical activity. A meta-analysis compiled by Hamer&Chida (2009) [5] highlighted that it is able to reduce the risk of AD by 45%. Alzheimer's disease is characterized by the loss of neuronal synapses and pyramidal neurons, which leads to progressive cognitive neurodegeneration [6]. The areas of the brain that are most affected by this disease are those associated with more complex brain functions, namely the hippocampus and the neocortex. There are several theories about the neuropathological changes that occur in AD, with accumulation of senile plaques and neurofibrillary tangles (NFTs) are the two main characteristic hypotheses. Senile plaques are mainly composed of insoluble amyloid β ($A\beta$) protein, specifically particularly its $A\beta_{42}$ isoform, which is formed by enzymatic cleavage of the transmembrane amyloid precursor protein (APP) [7]. These plaques accumulate extracellularly around neurons and glial cells. NFTs, on the other hand, are formed by hyperphosphorylation of the tau protein, which normally stabilizes microtubules in neurons [8].

Another factor playing a significant role in the development of AD is the inflammation that develops within the brain. In early stages of the disease, the immune response helps to clear A β plaques, thereby alleviating symptoms [9]. Microglia, the brain's immune cells, play a key role in this process by engulfing insoluble A β deposits via various receptors, such as CD36 and receptors for advanced glycosylation end products [10,11]. In addition, microglia activate extracellular proteases to degrade A β [12]. However, in advanced stages of AD, there is prolonged immune stimulation by A β , leading to a reduced efficiency of microglia in its removal [13]. This results in the release of pro-inflammatory products such as cytokines and reactive oxygen and nitrogen species, increasing A β production and tau hyperphosphorylation, resulting in neuronal damage and death [14,15]. This inflammation contributes to cognitive decline and disease progression. Understanding these neuropathological features and their interactions with inflammatory responses is crucial for the development of effective therapeutic as well as preventive strategies for AD. The current review describes the role of physical exercise as a preventive strategy for Alzheimer's disease. Physical activity plays a key role in maintaining brain health and preventing the negative effects of aging. There are many studies confirming the beneficial effects of regular exercise on cognitive function and delaying processes associated with brain degeneration. Aerobic training, which includes activities such as running, swimming, cycling or even fast walking, is a particularly effective form of physical activity for brain health. Studies have shown that people who regularly engage in this type of exercise have better cognitive function compared to those who those leading sedentary lifestyles [16].

Effects of physical activity on cerebral blood flow

There have been studies showing that patients with Alzheimer's disease experience a decrease in cerebral blood flow by as much as 40% compared to a control group [17]. The decrease in CBF is observed much earlier - at the first symptoms of cognitive impairment, which precedes the full-blown Alzheimer's disease by up to several years [18]. The decrease in CBF specifically involves regions of the brain such as the hippocampus, posterior cingulate nerve, and precuneus [17,18]. In a number of studies it has been shown that lower CBF as measured by ASL MRI indicates the rate of degradation of cognitive function in both healthy older adults and patients with AD [19,21,22]. In a study ADEX (ClinicalTrials.gov no: NCT01681602) researchers analyzed the effects of moderate- to high-intensity aerobic exercise or high intensity on cerebral blood flow in patients presenting with moderate or mild form of Alzheimer's disease. It involved randomization - 200 patients with mild or moderate Alzheimer's disease were randomly

assigned to either the exercise group or the control (standard care). MRIs were performed at the beginning of the study and after 16 weeks of regular exercise. The study showed that the described exercises had no effect on CBF regardless of their intensity, even though they may have positive effects on cognitive function. It supposes that CBF is not altered because the process of chronic hypoperfusion may be too advanced due to the fact that this phenomenon precedes the onset of AD symptoms for many years [23]. Patients with reduced CBF present worse MMSE scores and a possible reason for reduced CBF in these patients is the deposition of amyloid β in the cerebral blood vessels [24], which is a vasoconstrictor which reflects negatively on CBF - lowering it.

Physical activity - important, but not the only one in preventing AD

Dementia is not at all necessarily a natural consequence of the aging process. Many aspects are described related to lifestyle that can influence its development in older adults, both reducing its risk, as well as increasing it [25]. There are 9 main potentially modifiable risk factors affecting the development of dementia. They are: low levels of education, obesity, hypertension, hearing loss, smoking, diabetes mellitus, depression, social isolation, and the low level of physical activity already highlighted more than once in a given review, low levels of physical activity. In view of the fact that it is not possible to eliminate them completely, it has been concluded that the most important task is to influence the factors that can benefit the prevention of dementia, while their negative effects are highly unlikely. One of these factors is physical activity. A 2009 meta-analysis of 16 prospective studies included more than 160,000 members, confirmed that systematic physical exercise reduces the Alzheimer's disease risk by 45% [26]. In contrast, a 2012 study that analyzed for about three and a half years of 716 older people with preserved cognitive function, highlighted that high daily physical activity was associated with a more than 2-fold lower risk of AD compared to the analyzed subjects whose daily activity was low [27]. As for the impact of physical activity on people already diagnosed with AD or mild cognitive impairment (MCI), there are many discrepancies in research as to the improvement of cognitive function in these patients. Some studies show no significant difference in this aspect, others show a positive effect, and still others suggest the need for more standardized studies to assess this factor authoritatively [28,29]. Several of the studies evaluating the effect of regular aerobic exercise in individuals with baseline cognitive impairment (MCI) have shown improvements in cognitive abilities, as well as positive effects on these individuals' memory and executive functions [30,31]. It is particularly important to

influence cognitive function through physical activity in people with MCI, as this prevents further cognitive loss and also reduces the number of individuals subsequently developing AD. In people already diagnosed with Alzheimer's disease, and especially in the early stages of the disease, structured aerobic exercise affects favorably on the cognitive functions of affected individuals, especially their attention, executive functions and communication [32,33]. Suggesting from the results of the above studies, it can be concluded, that promoting physical activity is a very important aspect in delaying the onset of cognitive impairment among the elderly. In contrast, there are a number of studies that have pointed out that the elimination of one of the 9 main factors influencing the development of AD may be insufficient and overall lifestyle changes are needed, including the aforementioned physical activity, but also diet or cognitive training.

The effect of physical activity on the functioning of the gut-brain axis and the role of this system in the prevention of Alzheimer's disease

Recently, researchers have been directing their attention to disorders of the gut microbiota in the context of Alzheimer's disease. There is a theory of nerve inflammation, which explains the occurrence of the described disorder. According to the above theory, the immune system plays a special role in the development of AD in the form of astrocytes and microglia, which activation leads to increased production of pro-inflammatory cytokines responsible for the destruction of neurons in both the central and peripheral nervous system. [34,35]. The gut-brain axis includes more than 100 trillion microorganisms. These include, among others, Firmicutes, Bacteroidetes (90-95% of the intestinal microbiota), Actinobacteria and Cyanobacteria, and many others [36,37]. By the name of the so-called gut-brain axis, brain is referred to as the direct and indirect connection between the gut microbiota and the CNS, autonomic nervous system, the enteric nervous system and the hypothalamic-pituitary-adrenal axis. In addition, it involves multiple overlapping neuroendocrine and immune pathways. The functioning of these phenomena determines the development and proper functioning of neuronal pathways, influences cognitive abilities and brain aging. The microorganisms belonging to the gut flora metabolize complex carbohydrates to short-chain fatty acids (SCFAs) and these compounds are involved in various lipid metabolic processes that are crucial for microglia development [38]. SCFAs can also affect the synthesis of various neurotransmitters, which has a direct effect on cognitive functions throughout the body, for example, the presence of butyric acid and propionic acid results in the increased synthesis of serotonin, dopamine and norepinephrine which translates into the expression of hydroxylase tryptophan and tyrosine [39]. This fact

draws attention to the fact that keeping the gut microbiota in balance intestinal microbiota is important for the maintenance of normal cognitive functions of the individual through the indirect participation of bacteria in the synthesis of neurotransmitters. The following contribute to gut microbiota imbalance non-modifiable factors such as host genotype, age, sex but also modifiable factors, for example, smoking, alcohol, diet. Researchers have shown that disruption of this balance occurs in various neurological disorders, including Alzheimer's disease [40]. The phenomena described concerning imbalance of bacterial flora in the gastrointestinal tract can cause systemic inflammation of the body which in turn leads to excessive production of pro-inflammatory cytokines and activation of the microglia by which the blood-brain barrier becomes leaky [41]. Violation of the integrity of the intestinal barrier can lead to an influx of lipopolysaccharides (LPS) into the host's circulatory system. LPS is a highly acylated saccharolipid and a component of the membrane of Gram-negative bacteria. It provokes host immune system to respond and secrete pro-inflammatory cytokines and chemokines, as it is detected by the body's innate immunity, thus alerting it to the potential threats of pathogen invasion [42]. LPS, which is a component of the outer membrane of some bacteria, is detected by special receptors in the human body known as toll-like receptors (TLRs), including TLR4 and it can lead to the activation of immune cells immune system to produce pro-inflammatory substances, such as interleukin-1 β or nitric oxide and others, which lead to inflammation. These reactions take place in various cell types that are involved in the body's defense, such as microglia, astrocytes in the nervous system, and macrophages and leukocytes [43]. Researchers have reported that an important role in the imbalance of intestinal flora, that can be linked to AD are played by *Escherichia* and *Shigella* bacteria. They have been found to be present in stool samples and an increase in IL-1 β and CXCL2 expression in the blood of the patients studied [44]. At the same time, in various studies in people with cognitive impairment (including Alzheimer's disease) have found dysbiosis - an increase in *Escherichia/Shigella*, *Bacteroides* and *Ruminococcus* with a decrease in *Eubacterium rectale*, *Dialister* and *Bifidobacterium* [45,46]. In a study in a rat model of Alzheimer's disease, where rats were administered A β 1-42 peptide, the presence of this peptide was observed in their hippocampus, a brain region important for memory and learning. At the same time, significant changes in the gut microbiome - an increase in the number of bacteria that cause inflammation and a decrease in those that have an anti-inflammatory effect. In addition, the same study found that administration of fructooligosaccharides increased the presence of probiotics, such as *Lactobacillus*, and anti-inflammatory bacteria, such as *Bifidobacterium*, resulting in the

production of neurotransmitters such as acetylcholine, dopamine, serotonin and norepinephrine in the brain. This, in turn contributed to alleviating cognitive decline in animals that are models for the disease Alzheimer's [47]. Although there is a lot of knowledge about changes in the bacterial population in the gut and the link between them and the risk of Alzheimer's disease or neurological disorders is still rarely mentioned are the beneficial effects of physical activity on gut-brain processes and the brain and the progression of Alzheimer's disease. And the role of physical activity appears to be significant, as there is some evidence to suggest that moderate exercise promotes beneficial changes in the bacterial composition in the gut. For example, it has been shown that exercise can increase levels of certain short-chain fatty acids, such as butyric acid, and promote the growth of bacteria that show positive effects on gut health [48]. Studies have also shown that the microbiome of people who exercise regularly is characterized by greater diversity and the presence of bacterial taxa, in increased numbers than in people who do not exercise, producing butyrates such as Coprococcus, Clostridiales, Rosemaria, Lachnospiraceae and Erysipelotrichaceae [49]. It is the athletes who train regularly athletes, show an increased presence of the bacterium Akkermansia muciniphila in their microbiome, and this bacterium is associated with a lower risk of depression and Alzheimer's disease [50]. Mutual interaction between the gut microbiota and muscle training is particularly notable when the data clearly show the impact of both physical activity and exercise on the ecosystem of the gut microbiota. In general, regular exercise can induce changes in the composition of the gut microbiota, although these changes can vary depending on the intensity and length of the training, frequency, diet and metabolic state of the subjects

Effects of physical activity intensity on neuropsychiatric symptoms in patients with Alzheimer's disease

Numerous cohort studies indicate that physical activity in middle age protects against the deterioration of cognitive function and the development of dementia in old age [51]. In addition, it contributes to preserving the ability to perform activities of daily living in a group of older disease-free patients. In healthy individuals, a correlation was observed between the degree of intensity of physical activity and its effect on the body - higher levels of physical activity is associated with better cognitive performance [52]. Additionally, randomized studies involving patients with mild cognitive impairment (MCI) indicate a positive effect of physical activity of physical activity on one or more cognitive functions [53]. In a multicenter, randomized study "Preserving Cognition, Quality of Life, Physical Health and Functional Ability in Alzheimer's Disease : The Effect of Physical Exercise (ADEX)" involved 200 patients with mild forms of

Alzheimer's disease (AD), MMSE (Mini Mental State Examination) scores above 19, and in the range of 50-90 years of age [54]. Patients were randomized to either the intervention group or the control group. The intervention group performed 60 minutes of supervised aerobic exercise at moderate or high intensity three times a week for 16 weeks. In the control group, patients received pharmacological treatment in the form of antidepressants or mood stabilizers as before. In the intervention group, after a 4-week adaptation period, study participants were placed into moderate to high physical activity groups. The subjects with high physical activity had a training attendance exceeding 80% of maximum HR. The subjects with moderate physical activity, had an attendance exceeding 70% of maximal HR [55]. The primary measure of the test was the SDMT (Symbol Digit Modalities Test), which assesses mental speed and attention [56]. It also took into account other tests as well as the 12-item scale for assessing neuropsychiatric symptoms (NPI-12) [57]. In the study, no significant difference was observed between the groups (intervention and control) in the change in the primary SDMT score from baseline to the follow-up period. However, a significant difference was observed in the severity of the symptoms of the neuropsychiatric symptoms assessed with the NPI scale from baseline to follow-up, indicating less severe symptoms of the neuropsychiatric symptoms in the intervention group. The above data indicate that physical activity can have an impact on cognitive function, provided that high exercise frequency and intensity are maintained physical activity. This is evidenced by the fact that those with high physical activity showed a less decline in SDMT than the control group. The training intensity-dependent neuroprotective effect of physical exercise on cognitive function, may also depend on activity-related reduction in cardiovascular risk factors and other neuroprotective changes - an increase in factor cerebral origin, and reduction of proinflammatory cytokines [58,59]. From the data collected show that the study showed a significant change from baseline in neuropsychiatric symptoms neuropsychiatric symptoms in favor of the intervention group. In addition, an increase in the intensity of physical activity had a positive effect on reducing the severity of neuropsychiatric symptoms in patients with mild form of Alzheimer's disease.

Irisin - a myokine that may have an impact in the development of Alzheimer's disease

Irisin is a recently discovered molecule whose expression depends on the transcription factor PGC-1 alpha. To produce irisin, PGC-1 alpha is required for gene activation and production of a transcription protein called fibronectin domain-containing protein type III 5 (FNDC5), which, when cleaved, forms the precisely irisin [60]. Irisin acts similarly to hormones, which makes its role particularly fascinating. Irisin secretion is provoked by muscle contraction, so it is

considered a myokine associated with exercise. Its blood levels are closely linked to muscle work and volume. It is present in the brain - both in neurons and glial cells, as well as in other areas such as the hippocampus, cortex, hypothalamus and cerebellum [61,62]. Interestingly, endurance exercise stimulates the expression of the PGC-1 alpha / FNDC5 / irisin pathway in neurons, which may promote neurogenesis in the adult hippocampus by increasing levels of brain-derived neurotrophic factor (BDNF) [62]. BDNF signaling plays an important role in modifying connections between neurons (e.g., long-term potentiation, LTP), which is crucial for cognitive function, particularly in the hippocampal area. BDNF is also released during exercise, making it also a myokine that benefits the brain. For example, it has been shown that during exercise there is an increase in the BDNF expression in the hippocampus, leading to improved neuronal flexibility and spatial memory [63,64]. In addition, several studies suggest that irisin may have important potential for neuroprotective effects. For example, irisin use may protect the blood-brain barrier or hippocampal neurons from apoptosis in various ischemic strokes in rats, such as obstruction of the middle cerebral artery [65,66]. Both endurance (i.e., aerobic) and resistance (i.e., strength) exercise lead to increased FNDC5 gene activity and an increase in circulating irisin in both mice and humans [67,68]. Studies on the effects of physical training have systematically examined the relationship between physical activity, FNDC5/irisin gene and BDNF in the hippocampus [61]. It was found that the expression of the FNDC5 gene in hippocampal neurons is reduced in mouse models of Alzheimer's disease. However, the delivery of FNDC5/irisin to the brain via adenoviral therapeutics brought balance to the memory deficits and improved neuronal plasticity, such as LTP (long-term synaptic potentiation) [69]. Thus, the results of this study suggest that the beneficial effects that physical training brings to Alzheimer's patients may be mediated by irisin signaling. In a study on cultured astrocytes, irisin was found to have a protective effect on neurons against β -amyloid-induced toxicity and against cell damage. The described myokine provides neuronal protection by inhibiting the release of pro-inflammatory cytokines by astrocytes, such as IL-1 β and COX-2, by reducing the activity of the NF- κ B pathway [70].

Conclusions

Based on the review presented, it can be concluded that Alzheimer's disease is the most common type of dementia and is one of the main neurodegenerative disorders affecting the elderly. Given the significantly increasing incidence of Alzheimer's disease, researchers are looking for methods to prevent the development of this disease. Among the main protective factors are physical activity. Exercise helps improve cognitive abilities in older people elderly, regardless

of their initial clinical condition. Particular importance is attributed to aerobic as well as resistance training, of moderate intensity and lasting at least 45 minutes. One meta-analysis confirmed that systematic exercise reduces the risk of developing Alzheimer's disease by 45%. Studies evaluating the effects of regular aerobic exercise in people with baseline cognitive impairment (MCI), showed significant improvements in these abilities. In addition, physical activity reduces the number of MCI patients developing Alzheimer's disease in the future. In addition, attention has been drawn to the role of the gut microbiota, whose maintaining in balance is important for maintaining normal cognitive function. The role of physical activity also appears to be significant here, as moderate exercise promotes favorable changes in bacterial composition in the gut. Research suggests that the protein irisin may have important neuroprotective potential. The protein protects the blood-brain barrier and hippocampal neurons against neurodegeneration. The findings suggest that the beneficial effects that physical activity brings to Alzheimer's patients may be mediated by irisin-mediated signaling. The review found that in patients with mild cognitive impairment (MCI), physical activity has a positive effect on one or more cognitive functions. The neuroprotective effects of physical exercise depends on the intensity of the exercise - the higher the training intensity, the greater the protective effect on cognitive function. In addition, physical activity is associated with a reduction in risk factors serovascular and other neuroprotective changes - an increase in brain-derived factor, reduction of pro-inflammatory cytokines. Based on the data presented and the conclusions drawn from them, can be concluded that physical activity is one of the key factors in preventing the development of Alzheimer's disease and progression of cognitive impairment. In addition, it may be one of the strategy to prevent an increase in the incidence of the disease in the future, which has positive health, economic and social impacts.

Disclosures

Author's contribution

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