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THE ROLE OF SELECTED NUTRIENTS IN SUPPORTING PHARMACOLOGICAL TREATMENT OF ALZHEIMER'S DISEASE

Rola wybranych składników odżywczych we wspomaganiu leczenia farmakologicznego choroby Alzheimera

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A - Koncepcja i projekt badania, B - Gromadzenie i/lub zestawianie danych, C - Analiza i interpretacja danych, D - Napisanie artykułu, E - Krytyczne zrecenzowanie artykułu, F - Zatwierdzenie ostatecznej wersji artykułu

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Abstract (in Polish):
Choroba Alzheimera (AD, Alzheimer's disease) jest pierwotnie zwyrodnieniową chorobą mózgu o nie wyjaśnionej dotąd etiologii i złożonych procesach patofizjologicznych. Stanowi najpowszechniej występujący typ otępienia u osób starszych, które postępuje z biegiem lat i powoduje poważne deficyty funkcji poznawczych. Cechami neuropatologicznymi AD jest występowanie zwyrodnienia neurofibrylarnego i złogów amyloidu zewnątrzkomórkowego pod postacią blaszek amyloidowych. Oprócz szeroko opisywanych zaburzeń poznawczych czy objawów neuropsychiatrycznych otępienie

w chorobie Alzheimera prowadzi do postępującego wyniszczenia organizmu. Niedożywienie dotyczy nawet 25 % pacjentów z zespołem otępiennym. Badania wykazały, że dieta jest istotnym czynnikiem związanym z zapobieganiem pogarszania się funkcji poznawczych. Niektóre składniki pokarmowe takie jak witaminy B6, B12, C, A, E, kwas foliowy, kwasy DHA i EPA, cholina, selen, fosfolipidy, kwercytyna, S-allilocysteina mogą odgrywać istotną rolę w poprawie funkcji kognitywnych, spowalniać procesy neurodegeneracyjne w mózgu, oraz wspomagać farmakologiczne metody leczenia pacjentów ze zdiagnozowaną chorobą Alzheimera.

Abstract (in English):
Alzheimer's disease (AD) is originally a degenerative brain disease with an unexplained etiology and complex pathophysiological processes. It is the most common type of dementia among the elderly, which progresses over the years and causes severe cognitive deficits. The neuropathological features of AD are the occurrence of neurofibrillary degeneration and extracellular amyloid deposits in the form of amyloid plaques. In addition to widely described cognitive disorders or neuropsychiatric symptoms, dementia in Alzheimer's disease leads to progressive wasting of the body. Malnutrition affects up to 25% of patients with dementia syndrome. Studies have shown that diet is an important factor in preventing cognitive decline. Some nutrients such as vitamins B6, B12, C, A, E, folic acid, DHA and EPA, choline, selenium, phospholipids, quercetin, S-allylcysteine may play an important role in improving cognitive functions, slow down neurodegenerative processes in the brain, and support pharmacological methods of treatment of patients diagnosed with Alzheimer's disease.

Keywords (in Polish): choroby neurodegeneracyjne, Choroba Alzheimera, czynniki żywieniowe.

Keywords (in English): neurodegenerative diseases, Alzheimer Disease, nutritional factors.

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Wspomaganie leczenia farmakologicznego choroby Alzheimera

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Introduction

Alzheimer's disease (AD) is now a growing medical, social and economic problem. There are nearly 35 million patients in the world, but according to forecasts, this number will increase by 20 million in the next decade and will continue to increase [34, 63]. AD is originally a degenerative brain disease with not fully understood etiology and complex pathophysiological processes. It is the most common cause of dementia and primarily affects the elderly, over 65 years of age. At the beginning, neurodegenerative changes of the central nervous system (CNS) progress in a completely asymptomatic way, therefore, in most cases, the disease is diagnosed only on the basis of clinical symptoms, occurring with a significant degree of changes in the brain. Effective treatment of Alzheimer's disease requires early and accurate diagnosis, but pharmacological possibilities are currently limited. It is increasingly pointed out that proper nutrition can be a very important element preventing and supporting the treatment of AD [34]. A possible complement to classic AD treatment with cholinesterase inhibitors are nutraceuticals, i.e. nutrients whose deficiencies may initiate or accelerate the development of pathological changes within brain structures [53].

The aim of the study was to present current knowledge about selected dietary components affecting the improvement of cognitive functions in Alzheimer's disease.

For this purpose, using the keywords: „nutrients in Alzheimer's disease" and „role of nutrition in Alzheimer's disease", a review of publications from the years 2000-2022 was made using the Pubmed and Web of Science databases.

Docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA)

Both DHA and EPA are essential in CNS developmental and functional processes, including neuronal maturation, migration, neurogenesis, neurotransmission, synaptogenesis, and plasticity [58]. Research in recent years indicates that the mutual proportion of omega-6 to omega-3 acids in cell membranes is important for the effect of fatty acids on brain function [8]. Deficiencies in the diet of omega-3 acids cause the loss of DHA and an increase in the activity of PUFAs from the omega-6 family in the brain. This leads to disruption of neurogenesis, modification of protein activity, ion channels, transduction signals and gene expression. As a result, cognitive, behavioral and learning abilities are impaired [29]. There is growing scientific evidence on the effectiveness of n-3 LC-PUFA supplementation in neurodegenerative disorders such as AD. In a population study conducted in the Netherlands on a group of 5386 people (Rotterdam Study), it was shown that the consumption of fish rich in LC-PUFA n-3 was inversely proportional to the occurrence of dementia, in particular AD [30]. In a study conducted in the United States (Cardiovascular Health Cognition Study) on a group of 2233 people, it was found that eating fatty fish more than 2 times a week is associated with a 41% reduction in the risk of AD [28]. In France, in a study on the group 8085 (Three-City cohort study France) lasting three and a half years, it was shown that frequent consumption of fruits, vegetables, fish, oil rich in omega-3 acids reduces the risk of AD, especially among carriers of ApoE ε4 [5]. During the 7-year study of PAQUID (Personnes Agees OUID) in a group of 1416 older people (>68 years) from France, the effect of frequency of fish consumption on the risk of dementia was evaluated. Among people who consumed fish at least 1 time a week, a statistically lower risk of being diagnosed with dementia, including AD [6], was demonstrated. The correlation between low serum DHA content and the presence of AD was demonstrated by Conquer et al. [16]. In experiments conducted on older mice, it was shown that the reduced content of PUFAs in brain tissues caused memory loss, learning ability and visual impairment. The above effects of deficiency were significantly reversed as a result of supplementation of the mouse diet with fish oils, as well as DHA

itself [60]. According to Lukiw et al., DHA supplementation reduces the production and deposition of β-amyloid, the production of NPD1 neuroprotectin, which protects the nervous system through anti-apoptotic and neuroprotective mechanisms, increases. In addition, DHA reduces the phosphorylation of tau protein, affects the fluidity of cell membranes, and thus transmission [35].

Choline

Choline is an organic chemical compound classified as B vitamins (called vitamin B4) with an extremely important role in the human body. It participates in brain activity related to memory. Choline is a precursor to phosphatidylcholine (lecithin), the main component of cell membranes, as well as sphingomyelin. Choline after oxidation to betaine is a donor of methyl groups for homocysteine methylation and methionine synthesis [62, 27]. In addition, it participates in the synthesis of acetylcholine (Ach), an important neurotransmitter. However, endogenous choline synthesis is insufficient, in women it is 10-50% more efficient than in men, but stress increases the demand for it almost twice. The diet should therefore be supplemented with products rich in free choline and phosphatidylcholine, which include eggs, liver, beef, fish and milk. The optimal concentration of choline in the body affects the proper development of the fetal brain and cognitive functions. Supplementation with choline, vitamin B6, B12 and folate may slow down age-related cognitive decline [19]. Choline has also been found to exert neuroprotective effects by reducing or delaying the symptoms of cognitive impairment and memory loss that accompany aging. and occur in people with neurodegenerative diseases [18]. In clinical trials in patients with early AD, the combination of several methyl residue donors, including choline, vitamin B12, B6 and folic acid, improved memory and enhanced cholinergic signaling. The study authors indicated that the use of methyl donor combinations in patients provides essential precursors to enhance cell membrane integrity and cholinergic signaling [55]. Choline uptake from the bloodstream by the brain decreases with age, which requires an individual approach to patients in ensuring its adequate level in the body [15]. In summary, choline has been shown to play an important role in the proper development of the nervous system and neurocognitive functions. It is now considered a neuroprotective compound that, through epigenetic mechanisms, regulates the expression of key genes related to memory, learning and cognitive functions. Choline has also been proven to affect normal brain function and alleviate or delay cognitive deficit in the elderly or people with AD [9].

Phospholipids

In the human body, a special concentration of phospholipids occurs in the brain, where, together with LC-PUFA n-3, they are the basic building blocks of the nervous system. Sphingomyelin, classified as phosphosphingolins, occurs in large amounts in nervous tissue as a component of the myelin sheath of neurons [59]. The daily intake of phospholipids by an adult should be 2-8 g, which is 1-10% of the energy supplied with fats. Their rich sources are egg yolk, soybeans, pork and poultry liver [15]. The decrease in the amount of phospholipids in the brain associated with the aging of the body begins slowly after the age of 20, and after the age of 80 it becomes more pronounced. The results of the study show that there is a relationship between phospholipid deficiency and AD. In the brain of AD patients, reduced levels of phosphatidylinositol (PI), phosphatidylinositol-4, 5-bisphosphate and phosphatidylazitol-4-phosphate have been demonstrated, which determine the proper functioning of synapses. Reduced levels of phosphatidylcholine and phosphatidylethanolamine were also found, which leads to degeneration of structural phospholipids of the brain [33]. The degradation of phospholipids in the cell membrane

increases its rigidity, which affects the disorders in its functioning. Studies have shown that one of the causes of cognitive decline is a change in the lipid composition of nerve cell membranes, especially serine-containing phospholipids [24]. The results of the study document the importance of phosphatidylserine (PS) in reversing neurodegenerative changes [48]. In addition to building functions, PS acts as a cofactor of membrane enzymes affecting the activation of protein kinase C, which participates in the transmission of signals. PS also affects the concentration of acetylcholine, dopamine, norepinephrine and the increase in glucose levels in the brain, which helps in the proper functioning of the nervous system in the elderly [32, 36]. In clinical trials in people aged 50-90 years with memory impairment, who were given 300 mg of soy phosphatidylserine per day for a period of 12 weeks, an improvement in cognitive parameters was noted [42].

Vitamins B6, B12, folic acid

B vitamins and folic acid are essential in maintaining the proper functioning of the nervous system due to their key role in the conversion of homocysteine (Hcy) to methionine. Insufficient supply of these vitamins in the diet is often the cause of hyperhomocysteinemia, which is observed in patients with AD [61]. Homocysteine is a compound that has neurotoxic effects, contributes to the development of cognitive disorders and dementia of vascular and neurodegenerative origin. Persistent elevated homocysteine levels lead to vascular endothelial dysfunction and increased chronic inflammation. This is a direct result of the strong oxidative stress that accompanies hyperhomocysteinemia. Ischemia resulting from narrowing of the brain microvessels may stimulate amyloidosis and increase the risk of AD [22, 31]. Homocysteine also increases the susceptibility of neurons to oxidative stress [12]. Elevated serum homocysteine levels are also associated with altered DNA methylation patterns found in AD patients [4]. Insufficient intake and/or age-related changes in the absorption and metabolism of vitamins B12, B6 and folate may cause disturbances in the homocysteine transformation cycle and, as a result, hyperhomocysteinemia [4]. It was shown that homocysteine concentrations above 14 μmol/l were significantly associated with twice the risk of AD development [61]. Numerous studies indicate that low levels of cobalamin, pyridoxine and folic acid in the blood are associated with an increased risk of developing AD, while supplementation of these compounds is associated with improved cognitive functions in the elderly [41].

Antioxidant vitamins

The mechanism underlying the development of AD is oxidative stress. The most important antioxidant vitamins, the supplementation of which may contribute to the prevention and support of pharmacological treatment of AD include ascorbic acid (vitamin C), α-tocopherol (the active form of vitamin E), carotenoids and retinol (vitamin A) [40]. A meta-analysis evaluating 51 studies comparing blood plasma nutrient levels in people with AD and those without cognitive impairment showed that AD patients had significantly lower levels of vitamins A, C, E, α-carotene, β-carotene, lycopene, and lutein [40]. A study of all forms of vitamin E in plasma and markers of vitamin E damage, conducted among 168 patients with AD, 166 with mild cognitive impairment (MCI) and 168 healthy subjects, indicated that low levels of tocopherols and tocotrienols indicate an increased likelihood of AD and MCI [38]. Among the 5395 participants in the Rotterdam Study over 55 years of age, the intake of oxidative vitamins was assessed. During the 6 years of research, 197 cases of dementia were shown, of which 146 people were diagnosed with AD. It was shown that high intake of vitamins C and E was associated with a low risk of AD, regardless of the presence of the APOE genotype [61]. Literature data indicate vitamin

deficiencies in the elderly as a result of poor digestion, absorption and metabolic disorders. Vitamin A deficiencies are most often accompanied by protein malnutrition leading to a decrease in retinol-transporting proteins in the blood serum [18]. A study among 4740 patients over the age of 65 showed that dietary supplementation with vitamins C and E had an impact on the reduction of AD incidence [7]. Many studies show that antioxidants may also contribute to improving cognitive function in older people [40].

Selenium

Due to the fact that oxidative stress plays a large role in progressive dementia and Alzheimer's disease, selenium with its antioxidant properties is considered a potential therapeutic agent. The level of selenium in the brain is relatively constant even under conditions of selenium deficiency. The brain is supplied with selenium by selenoprotein P (SelP), and the receptor for SelP is ApoER2 [1]. Studies conducted on rodents have shown that selenium inhibits oxidative stress in brain cells, protects against neurodegeneration and counteracts deregulation of signaling mechanisms [49]. The role of selenium in the form of sodium selenate in the metabolism of β-amyloid and neuronal death induced by this peptide has also been confirmed [26]. In studies investigating the effects of chondroitin sulfate (SeCS) nano-selenium on Alzheimer's disease in mice, SeCS was found to reduce anxiety, improve spatial orientation, memory and learning ability. In addition, the level of superoxide dismutase (SOD) and glutathione peroxidase (GPx) increased, and cellular oedema and pycnose decreased. The results of the Western blot analysis showed that SeCS can inhibit excessive phosphorylation of tau protein [21]. A randomized, double-blind clinical trial involving 79 AD patients investigated the effects of concomitant supplementation with probiotics and selenium on patients' cognitive function and metabolic status. For a period of 12 weeks, patients supplemented each day with 200 μg of selenium and probiotics containing Lactobacillus acidophilus, Bifidobacterium bifidum and Bifidobacterium longum at a dose of 2 x 109 CFU each. Concomitant supplementation with selenium, selenium and probiotics improved cognitive function in patients (according to the MMSE scale), the level of highly sensitive C-reactive protein (hs-CRP), insulin, triglycerides and LDL cholesterol in blood serum was significantly reduced [56].

Quercetin

Quercetin is classified as flavonoids with very strong antioxidant properties. It is found in green tea and as a natural plant dye in many fruits and vegetables. The antioxidant properties of quercetin are mainly due to its ability to capture free radicals, the ability to chelate metal ions. Quercetin can modulate biochemical pathways involved in neurogenesis and neuronal survival. For example, the Nrf2-ARE pathway can modulate the formation and degradation of misfolded protein aggregates present in AD [17, 23]. Quercetin has been shown to selectively eliminate senescent cells in the brain of mouse models with AD, suggesting that quercetin has senolytic effects [47].

SAC

One of the main compounds present in mature garlic extracts (AGEs) and extracts of black garlic is S-allylcysteine (SAC), a compound derived from allicin present in fresh garlic [37]. Studies in mouse models of Alzheimer's disease treated with AGEs and SAC have shown the important ability of these compounds to reduce Aβ and tau protein toxicity. SAC can prevent neurodegeneration caused by Aβ

toxicity in the hippocampus by alleviating endoplasmic reticulum stress and inhibiting caspase 3 activation, which reduces synaptic function and postsynaptic density. In transgenic mice treated with AGEs, improvements in memory and learning ability were observed [2, 52]

Applications

For many reasons, such as physical, cognitive, emotional and social state, older people may develop nutritional deficiencies more quickly. Polish research conducted on the elderly indicates difficulties in maintaining a properly balanced diet, which leads to malnutrition and contributes to a faster onset of dementia symptoms. Pharmacotherapy support for patients with dementia and AD can be expected from dietary interventions contributing to changes in neurotransmission [30]. Many components of the diet can modulate the biochemistry of the central nervous system (CNS), the anti-aggregation properties of Aβ and tau, and anti-inflammatory properties, thereby slowing down the neurodegenerative processes of the nervous system.

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