Review article

Nutrition Patterns in Prevention and Treatment of Neurodegenerative Diseases: Alzheimer's Disease

Vesna Šeper [1], Nebojša Nešić [1]

[1] College of Applied Sciences "Lavoslav Ružička" in Vukovar, Croatia

Corresponding author: Vesna Šeper, vseper@vevu.hr

Abstract

Background: The population of the elderly is increasing, as is the number of people suffering from neurodegenerative diseases. Since the cause of those diseases is unknown, there is no appropriate medical treatment. The purpose of this systematic review is to present papers on consumption of certain foods, supplements or introduction of dietary restrictions that promote healthy brain aging or possibly delay the onset of disease.

Methods: The PubMed, ScienceDirect, and SpringerLink databases were used for the research. 24 studies with a total number of 10 445 participants were selected as satisfying the final criteria.

Results: Mediterranean diet, dietary supplements and natural nutrients with recently discovered pharmacological properties are of interest to numerous scientists.

Conclusion: Since the results of the studies are inconsistent, we concluded that a large, carefully controlled long-term interventional study would be required in order to investigate the effect of nutrition on prevention of disease and cognitive decline.

(Šeper V, Nešić N. Nutrition Patterns in Prevention and Treatment of Neurodegenerative Diseases: Alzheimer's Disease. SEEMEDJ 2019; 3(1); 42-49)

Received: March 26, 2019; revised version accepted: May 16, 2019; published: May 31, 2019

KEYWORDS: Alzheimer's disease, inflammation, amyloid plaques, berries, supplements

Introduction

The number of people who are over 65 is growing and it is estimated that said age group will constitute up to 30% of the entire world population by the end of 2050. Aging includes changes to all organs and body systems, as well as to the brain. In 2001, there were 24 million people in the world older than 60 and suffering from dementia. It is estimated that this number will double every twenty years and that by the end of 2040 80 million people will be suffering from it (1). The economic burden of care and treatment of neurodegenerative diseases also increases the need for seeking measures for prevention or reversing of age-related disorders (2). A neurodegenerative age-related disease like Alzheimer's (AD) appears to be the consequence of stress and of the same environmental factors that are responsible for the aging of other organs and body systems. The clear cause of the disease is still unknown, but some key changes, including membrane/synaptic degeneration and abnormal protein processing resulting in the formation of amyloid-β plaques and neurofibrillary tangles, have been detected (3). Oxidative stress and inflammation are thought to play a significant role in the early stage of the disease, forming a vicious circle of damaging the sensitive brain cells. Epidemiological studies point out that anti-inflammatory, antioxidant and neuroprotective agents found in food or plants may have a positive effect by strengthening the neuronal antioxidant defence. The Mediterranean diet has also been linked with a lower incidence of neurodegenerative diseases such as AD (4). Neurodegenerative diseases cannot be prevented using specific medication or treatment, so identifying a new natural compound with pharmacological properties is the subject of interest to a large number of scientists. Chronic neurodegenerative diseases like AD and Parkinson's disease are related to obesity and diabetes, not just in the developing countries, but in the developed countries as well. Dietary restrictions, including a diet low in saturated fats, cholesterol and carbohydrates and the consumption of berries, nuts and neuroprotective plant supplements, might have a positive effect on healthy brain functioning (5, 6).

Burgener et al. (2008) state that some people live to be 90 and have adequate cognitive functioning while some develop symptoms of AD in their late 50s. The difference might be due to interaction between genetics and environment (1). Since we cannot fully affect genetics, this review will focus on actions promoting healthy brain aging and possible delay of the onset of the disease, including the consumption of certain foods, supplementation and introduction of dietary restrictions.

Methods

Literature research took place in January 2018. Databases used in the search were PubMed, ScienceDirect and SpringerLink. Keywords neurodegenerative diseases, prevention, Mediterranean diet, nutrition, supplementation were entered to identify papers dealing with neurodegenerative diseases and nutrition. The PubMed database yielded 2 articles. Another 102 articles were found after using the option "similar results" with the first paper and 98 articles were found for the second paper.

Inclusion Criteria

All articles containing the terms Alzheimer's disease, neurodegenerative diseases, dementia, cognitive decline, mild, Mediterranean diet, nutrition, vitamin B, C, E, D, antioxidants, supplementation, MUFAs, PUFAs, ω-3, ω-6, olive oil, prevention, cohort, prospective in the title or abstract were included in the review. If terms physical activity, cancer, cardiovascular diseases, respiratory problems, drugs appeared in the title or abstract of the article, they were excluded. Other exclusion criteria were if a paper included animal research (dogs, rats), if it tested medicinal dietary supplements or if it could not be fully accessed.

The criteria were ultimately met by 24 articles regarding studies conducted on 10 445 participants.

Results

The final results obtained after applying filters are shown in Table 1.

Table 1. PubMed search methodlogy and results

FILTERS	PAPER 1	PAPER 2
similar results	102 new articles	98 new articles
from 2000 until 2018	97	98
on humans	92	96
English language	85	87
persons 65+	16	21
review of abstracts and title of the articles based on including criteria	8	7

The same keywords were used to search the ScienceDirect database and 430 articles were identified initially. This number was narrowed to 372 after setting the timeframe to include articles published from 2009 to 2018. The number of articles was further reduced to 69 by using the option "type of article – research" and to 11 by using the option "publication title". They were published in the journals Clinical Nutrition, Alzheimer's & Dementia and Food Research International. After reading the titles and abstracts, 4 articles were selected.

The above-mentioned keywords were used for searching the SpringerLink database, where 264 articles were identified. After applying the filter article, the initial number was reduced to 177 and then to 23 after using the filter "biomedicine". Further restriction of results was accomplished using the options "Neurosciences and English", which led to 10 articles. Titles and abstracts were reviewed, and 3 articles were selected.

Discussion

Neurodegenerative diseases and nutrition

Dry matter in the brain mostly consists of fat, 20% of which is made up of ω-3 and ω-6 polyunsaturated fatty acids, which significantly influence the structure and composition of the neuronal membrane. Adequate nutrition is the source of those acids. Aging brings changes in the taste and smell of food, the basal metabolic rate decreases, and due to possible swallowing impairment and impaired digestion, dietary intake is also reduced. Unsaturated fatty acids and vitamins are thus in deficit. Neuronal membrane lipids change and influence homeostasis necessary for membrane fluidity and function, as well as for prevention of loss of synaptic plasticity, apoptosis and neurodegeneration (3). Since the cause of neurodegenerative diseases is still unknown, numerous researchers have made speculations regarding the connection between dietary habits, food intake and aging as the possible link for prevention or delay of the onset of neurodegenerative diseases, especially AD (7). Particular attention was given to diets such as the Mediterranean diet, food supplements and introduction of dietary restrictions.

Mediterranean diet

Notably, there are few published studies dealing with primary or secondary prevention of AD through nutritional interventions. Most of them have focused on the effects of single nutrient supplementation (3). However, studies should focus on the entire dietary pattern and not just on a single nutrient in order to avoid neglecting important interactions between food components since people do not eat only single

nutrients (7). After analysing a number of dietary patterns, the Mediterranean diet was selected. This type of diet is characterized by consumption of fruit and vegetables, legumes, fish and complex carbohydrates on a daily basis. Olive oil is the main source of fat, and moderate drinking of red wine at meals is recommended (7). One of the first studies linking the Mediterranean diet to a lower risk of developing AD was conducted in 2006 in New York on 2258 non-demented participants. After 4 years of follow-up, the results showed that higher adherence to this type of diet lowers the risk of developing AD, which indicates that that such diet may have a protective effect (8). Anther cohort study, the Washington Heights/Hamilton Heights Columbia Aging Project (WHICAP) conducted in 2012 on 1219 non-demented people, found that higher levels of ω-3 polyunsaturated fatty acids from fish, poultry, nuts and margarine were significantly associated with lower levels of plasma Aβ42, which suggests that they play an important role in lowering the risk of AD and slowing cognitive decline (9). Consumption of at least 100 grams of olive oil per day as one of the sources of polyphenols also slows cognitive decline (1). Morris et al. (2015) studied the connection between the MIND diet, a hybrid of the Mediterranean diet, and the occurrence of AD. The MIND diet contained 15 nutrients, 9 of which were linked to healthy brain aging (leafy greens, nuts, berries, legumes, whole grains, fish, poultry, olive oil, red wine) and 6 to unhealthy brain aging (red meat, margarine, cheese, pasta, sweets, fried food). The study was conducted on participants of the Rush Memory and Aging Project (MAP) in Chicago from 2004 until 2014, which included 923 people aged 58 to 98. The results showed that even moderate adherence to the MIND diet has a protective effect, significantly lowering the number of AD cases. This does not necessarily mean that the MIND diet is specifically effective for AD, but that it has a protective effect on the brain and general functioning (10). Fruit and vegetable consumption typical for the Mediterranean diet showed a link with lower risk of AD and dementia in women, while consumption of fish and seafood significantly correlated with lower incidence of dementia in general among the people of southwestern France (11). The Mediterranean diet, alone or in combination with other dietary patterns, represents the most effective approach to slowing the progression of AD with the fewest possible adverse effects (11). Persons who adopt this type of diet are less likely to develop AD than their peers who do not (12).

Supplements and their role

Vitamins are important for normal functioning of the whole body, including the brain. Therefore, the American Food and Drug Administration Agency mandated fortification of grains with folate from 1996 until 1997 to prevent vitamin deficiency (13). It is believed that a deficiency of folic acid and other B vitamins, along with vitamin C and E deficit, can contribute to the development of AD (14). However, results of vitamin supplementation are inconsistent. A longitudinal cohort study conducted on 965 people over 65 years in New York (northern Manhattan) suggests that lower risk of AD development is associated with total folate intake from both food and dietary supplements, rather than intake from a single source, while intake of vitamins B6 or B12 is not linked to or significant for the risk of AD (13). Similar results were obtained in a cross-sectional study conducted on 1219 cognitively healthy people older than 65, where no significant link was found between lower risk of AD and vitamin B9, B12, C, E and β-carotene supplementation (9). A longitudinal cross-sectional study conducted on 4470 participants (the Cache County Study) aimed to determine the link between antioxidant supplementation and the risk of AD development. Previous studies reported that vitamins C and E act neuroprotectively and lower the risk of AD by scavenging free radicals and other reactive oxygen species (15). A longitudinal study in Sweden involving 1810 people older than 75 (Kungsholmen Project), conducted from 1987 to 2000, identified that lower levels of vitamin B12 and folic acid, probably due to malnutrition or malabsorption in the elderly, double the risk of AD (16). Vitamins B9 and B12, unlike vitamins C and E, regulate

homocysteine levels in the blood, which are associated with the risk of AD. A multicentre randomized double-blind controlled clinical trial conducted in America (ADCS) from 2003 until 2006 on 340 participants reported that high dosage of vitamin B6, B12 and folic acid supplementation did not delay cognitive decline, nor did it improve the clinical status of persons with mild or moderate AD (17). The discrepancy of results may be due to the different mechanisms of action of vitamins in prevention of AD, the number of participants and their age, the type and duration of the study, pre-existing vitamin deficiency and the type of prevention involved (primary, secondary or tertiary). Berti et al. (2015) conducted a cross-sectional study on 52 participants at risk of developing AD from 2013 to 2014 to clarify how nutrients are associated with healthy brain aging and prevention of AD. The objective was to identify how different patterns of nutrition affect the formation of Aβ plaques (initial sign of pathological changes), glucose metabolism (indicator of neuronal activation) and grey matter volume of the brain (sign of atrophy). The results showed that higher intake of vitamins B12, D and Zn reduces Aβ plaque load in the brain, as well as increases neuronal activity and grey matter volume. Higher activation of neurons was registered during higher intake of vitamin E, ω-3 and ω-6 polyunsaturated fatty acids, vitamins A, C and whole grains. Intake of vitamins B 1, 2, 3, 6, 9 and minerals Ca, Fe, Mg, P, K, Se showed no significant effect on the formation of Aβ plaques, neuronal activation and grey matter atrophy, while higher intake of saturated fatty acids, food high in cholesterol and sodium had a significant impact on lowering neuronal activation and grey matter volume (18). Results obtained from a small number of carefully screened subjects in another large cohort study (Three-City Study) conducted in three French cities from 1999 and 2000 until 2012 on 9294 people, only 666 of whom were non-demented, confirmed that there is a strong link between lower intake of vitamin D, carotenes and polyunsaturated fatty acids, higher intake of saturated fatty acids and long-term risk of AD and dementia. Future interventional research on primary prevention of AD and dementia should focus on the optimal combination of nutrients based on the results obtained so far (19).

Polyphenols

This paper did not focus on the effects of polyphenols on animals, only on humans. Vitamin P was first mentioned in 1936, and has been plentiful in the human diet since then. Polyphenols are secondary plant products believed to have a positive effect on human health, particularly for the elderly (20). Polyphenols from different fruit such as blueberries, blackberries, grapes and apples, from green and black tea, wine, coffee, cocoa and from spices such as turmeric and curry possess anti-inflammatory, antioxidant and neuroprotective properties (21). Research on polyphenols in Japan and Singapore has indicated that they have the potential to be neuroprotective (12), although the underlying mechanisms have not been fully clarified. Polyphenols interact with a wide range of neurotransmitters, suppressing neuroinflammation and degeneration through direct, indirect or complex action (22). Since 1936, almost 10 000 articles have been published on the chemical nature and biological activities of polyphenols (20), suggesting that they have a neuroprotective effect. Evidence from first-in-human research has identified that polyphenols have a positive effect, as part of a balanced diet. However, the effects of antioxidants have been disputed in the past few years. It has been suggested that their metabolites do not cross the blood-brain barrier, which brings their neuroprotective effect into question (20).

Caloric restrictions

The average energy requirements for an adult person are 25 kcal/kg/day. They decline after adolescence because the human body stops growing and basal metabolic rate decreases. Between the ages of 55 and 75 energy requirements decrease by 8% for every decade and by an additional 10% for every decade after 75 (23). Caloric restriction as a way of primary

prevention of AD may be used only in those individuals with normal eating patterns. Malnutrition and weight loss are usually associated with the onset of AD; caloric restriction would thus be counterproductive (23).

Discussion

Although no cure for neurodegenerative diseases exists, prevention and delaying the onset of the diseases is important. Large cohort studies have confirmed the protective role of diets like the Mediterranean diet, of a higher intake of polyunsaturated instead of saturated fatty acids, of a higher intake of fish and of vitamin supplementation (24). The role of decreased levels of a single nutrient and its supplementation in prevention of cognitive decline and dementia are eliciting controversy, probably because supplements act in a synergistic way and single nutrient supplementation will not lead to improvement (25). Seven lifestyle risk factors have been identified in connection with AD. Besides low education, physical inactivity, smoking, depression and hypertension, the role of nutrition is the most controversial and the role of sleeping disorders has not been sufficiently researched (26). A carefully controlled long-term interventional study on the effects of diet on prevention and delaying the onset of disease is required (24), with special consideration given to participants, type and duration of study, biomarkers for AD and intermediate outcomes (26).

Conclusion

The most investigated nutrients in regard of AD and cognitive decline are ω-3 and ω-6 polyunsaturated fatty acids from fish, poultry, nuts and margarine, as well as, folic acid, vitamin C and E. Consumption of polyphenol-rich foods like blueberries, blackberries, grapes, apples or beverages such as green and black tea, coffee and red wine may be beneficial. Adherence to Mediterranean diet is recommended because of the protective effect on the brain and general functioning. Caloric restriction may be counterproductive in elderly. Future intervention studies aiming to influence the modifiable lifestyle factors and to reduce the number of people at risk for AD, or at least slow down cognitive decline, are required.

Acknowledgments

The authors would like to express sincere gratitude to Professor Sergej M. Ostojić, MD, PhD, Vice-Dean for Scientific Research at the Faculty of Sport and Physical Education Novi Sad for his advice and instructions. They would also like to thank Biljana Rodić, MD, PhD, Head of the Neurology Department and Stroke Unit of the Cantonal Hospital Winterthur for the advice concerning neurodegenerative diseases.

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