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Omega-3 and Memory Function: To Eat or Not To Eat

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Abstract

At present it is estimated that 25% of the population older than 85 years have significant cognitive impairment. The global prevalence of cognitive impairment and dementia including Alzheimer's disease is expected to rise significantly in proportion to increased life expectancy. Deterioration of memory function and ultimately establishment of Alzheimer's disease (AD) severely debilitates the affected individual, uncompromisingly decreasing the quality of life of both affected patients and their care givers. Moreover, the cost of providing adequate care to patients with AD is a significant burden to both family and the health care providers. Therefore, various attempts have been made to identify means of either delaying the onset of cognitive impairment or improving memory function in patients affected by AD. Among a number of participants, importance of dietary fatty acids in particular omega-3 based fatty acids have gained significant momentum. This article aims to review published evidences for the role of omega-3 in memory function.

Keywords

cognitive impairment, Alzheimer's disease, dietary fatty acids, omega-3, docosahexaenoic acid

Dementia and Alzheimer's Disease

Dementia is fast becoming a major public health issue due to an increase in life expectancy and the ever increasing number of the aged in the population. Alzheimer's disease (AD), the most common form of dementia in the elderly population, is a progressive neurodegenerative disease characterized by impairment of memory, judgement, attention span, problem-solving skills, followed by severe apraxia (impaired motor activity) leading to abolishment of independence in affected individuals. This in turn has a major negative impact on the quality of life of both affected patients and their care givers. The causes of AD are unknown and believed to be complex and multifactorial in nature, possibly consisting of diet, lifestyle, vascular, genetic, and amyloid related factors.[1,2] The neuropathological features of AD include intraneuronal neurofibrillary tangles containing abnormally phosphorylated tau protein, extracellular β-amyloid plagues, and functional impairment of neurotransmitter system.[3]

The prevalence of dementia increases with age, doubling every 5 years.[4,5] An estimated 683 597 people in the United Kingdom have dementia. This number is said to rise to 800 000 and is forecasted to increase further to nearly 1 million by 2021 and approximately 1.7 million by 2051.[5] In the United Kingdom, on average, dementia is said to cost £25 472 per person due to care (home and day care) and dependency. It is claimed that 10% of deaths in men older than 65 years and 15% of deaths in women older than 65 years might be due to dementia, which is a staggering 59 685 deaths per year, a number that can be halved to 30 000 per year if the onset of dementia were to be delayed by 5 years.[5] Furthermore, as the life expectancy increases, the prevalence of AD is expected to rise with greater burden on health care providers. Although AD is a progressive and irreversible disease, various studies have indicated that cognitive impairment in early stage of AD is mostly due to synaptic dysfunction caused by soluble oligomeric Ab peptide, while widespread synaptic loss and neurodegeneration occurs in established late stages of AD.[6-10] Thus, early intervention even in mild cognitive impairment may be the key to providing effective therapy and reducing number of deaths due to dementia.

Life Style and Nutritional Impact on Cognitive Function

The true impact of life style on memory function is not fully understood yet. In fact, contrasting reports have added to this uncertainty. Nonetheless, several human studies have shown a clear association between high-fat diet, high intake of refined sugar, lack or reduced dietary intake of vegetables, obesity, and development of AD.[3,11-13]

It is generally believed that nutrition could offer ways of delaying the onset of AD or slowing its progression. Although

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epidemiological data on the role of specific constituents of the diet in reducing the risk of dementia remains inconclusive, recent publications point to the importance of low-fat, low-calorie diet on reducing risk of AD. For example, a 7-year follow-up study involving 8085 nondemented participants aged 65 and older and 281 incident cases of dementia found frequent (2 to 3 times a week) consumption of fruits and vegetables, fish, and omega-3 rich oils to significantly decrease the risk of dementia and AD.[14] Another very recent prospective study of 1880 community-based participants from 1992 to 2006 reported positive impacts of Mediterranean dietary habit and high physical activity in reducing risk of cognitive decline. Indeed, combination of physical activity with Mediterranean diet (high in fish, fruit, and vegetables and low in meat and dairy products) significantly reduced absolute risk of AD by 12% (21% in the group with no physical activity and low Mediterranean diet vs 9% in the group with high physical activity and Mediterranean diet).[15] These findings were irrespective of sociodemographic, vascular risk factors and the Apolipoprotein E (ApoE) genotypes. Similar studies have also reported markedly significant inverse association with adherence to Mediterranean diet and progression of AD. A case-control study nested within a community-based cohort in New York has also indicated higher adherence to Mediterranean diet is significantly associated with lower risk of AD.[16] Moreover, in another study of a multiethnic cohort, a higher adherence to Mediterranean diet was reported to be significantly associated with a reduced risk of developing mild cognitive impairment and with a reduced risk of conversion of mild cognitive impairment to established AD.[13] These reports indicate Mediterranean diet per se as a protective factor against cognitive dysfunction after adjusting for age, sex, ethnicity, educational level, ApoE genotype, caloric intake, and body mass index.

Apolipoprotein E belongs to the family of plasma lipid-binding proteins involved in triglyceride and cholesterol transport and delivery.[17] This protein also contributes to the clearance of Amyloid beta (Aβ) peptide through binding to lipoprotein receptors. Certain lipid molecules may play a role in the pathogenesis of AD possibly by preventing the production of Aβ peptide and hence its deleterious effects. Furthermore, neuronal cell death induced by Aβ oligomers involves lipid mediators such as sphingosine-1-phosphate, an anti-apoptotic molecule able to inhibit Aβ-induced neuronal apoptosis and arachidonic acid-dependent pro-inflammatory pathway,[17,18] indicating importance of lipid profile in preserving neuronal cell function. Interestingly, in 1 study, the protective effect of fish consumption against all-cause dementia was found only among ApoE ε4 noncarriers,[14] suggesting existence of multifactorial and complex systems involved in preserving neuronal longevity and their functionality.

Omega-3 and Cognitive Function

Generally, polyunsaturated fatty acids (PUFA) are assumed to have a positive effect on health. Several studies have shown omega-3 fatty acids to have beneficial effects on neuronal functions, inflammation, oxidation, vascular function, and cell death.[1,19-21] The conflict remains as to whether intake of omega-3 fatty acids which are largely found or associated with fish consumption protects against memory loss. A variety of preclinical and clinical studies have aimed to elaborate further on the effectiveness of dietary omega-3 on cognitive function. The mechanisms of action of omega-3 includes increasing substrate-saturation of low-affinity enzymes involved in the synthesis of phosphatides.[22] Indeed, addition of omega-3 polyunsaturated fatty acid docosahexaenoic acid to diet increased brain phosphatides (crucial to optimal brain function and neuronal cell membranes) levels, enhanced neurotransmitter release, and improved cognition.[23] This hypothesis is however not supported by others. In both transgenic and nontransgenic mice, dietary omega-3 had failed to improve cognitive performance despite increase in brain omega-3 levels, indicating lack of efficacy of omega-3 as a protective agent against cognitive dysfunction.[24] Of course, it is important to note that these discrepancies may be due to differences in experimental conditions. Furthermore, it is possible that genetically homogenous animals might have a nonresponsive genotype that may account for lack of sensitivity to nutritional factors unlike heterogeneous human participants.

Clinical studies have also been inconclusive on reporting beneficial effects of dietary omega-3 on memory function. A randomized double-blind placebo-controlled study on 32 participants with mild or moderate AD and 23 mild cognitive impairment found that omega-3 significantly improved cognitive portion of Alzheimer Disease Assessment Scale (ADAS-cog) compared with the placebo group in participants with mild cognitive impairment though this improvement was not observed in participants with mild or moderate AD.[25] Similarly, a significant reduction in cognitive decline as measured by Mini-Mental State Examination (MMSE) and "delayed word recall" subitem of ADAS-cog in patients with very mild cognitive dysfunction were observed in participants receiving omega-3 fatty acid.[26] These reports suggest that omega-3 has a positive protective effect only in participants with very mild cognitive impairment but not those with mild-to-moderate AD. Furthermore, a recent publication from Canadian Study of Health and Aging (CSHA) also failed to show any protective association between omega-3 fatty acids or eicosapentaenoic acid (EPA) and risk of dementia.[27] A similar cohort study (Rotterdam Study) has also failed to find a protective effect of moderate consumption of oily fish and omega-3 fatty acids in alleviating risk of long-term dementia.[28] In this study, 5395 nondemented participants older than 54 at baseline were recruited with follow-up period of 9.6 years during which 465 participants developed dementia, with 365 being diagnosed with AD. The data analysis indicated that neither high fish intake nor consumption of dietary omega-3 reduces risk of developing dementia.[28] Interestingly, others have reported very conflicting findings regarding the role of omega-3 in cognitive function. The Three-City Study from Bordeaux (France) where 1214 nondemented participants were followed up for 4 years reported that high plasma concentrations of EPA may

decrease risk of dementia while those of omega-3 and arachidonic acid may increase the risk of dementia.[29]

Docosahexaenoic Acid and AD

The pathological signs of AD which include cognitive impairment, loss of synaptic marker, hyperphosphorylation of tau, and Amyloid beta accumulation are susceptible to the effects of docosahexaenoic acid (DHA).[30] Docosahexaenoic acid is an omega-3, essential polyunsaturated fatty acid in the central nervous system essential for the development and maintenance of prenatal brain and maintenance of vision in adults.[31] It is predominantly found in marine fish and algae, is a major constituent of neuronal membranes, and functions to prevent neuronal cell-death through various protective mechanisms.[32] Patients with established AD have decreased levels of DHA in their brain membranes[33,34] suggesting an association between neuronal DHA levels and cognitive function. Indeed, a number of published literatures indicate a direct relationship between high levels of DHA and improved cognitive function in patients with AD. Both preclinical and clinical studies have reported that increased intake of DHA-rich fish prevents the development of AD and at worst ameliorates cognitive decline.[17,35-37] The beneficial effects of DHA have also been reported in animal studies. In transgenic animal model of AD, high dietary DHA markedly (70%) reduced total Aβ protein compared with their chow-fed counterparts[38] suggesting that dietary DHA limits beta-amyloid production, thus reducing plague burden, by decreasing its accumulation and toxicity and ultimately preventing synaptic loss.[39]

The mechanisms of action of DHA includes preventing cytoskeleton perturbations, caspase activation and apoptosis,[37] and by promoting extracellular signal-related kinase–related pathways and thus inducing changes in neuronal membrane properties and increasing protection from soluble Aβ oligomers.[40] The loss of postsynaptic proteins, typically seen in AD, is associated with increased oxidation.[37] Oxidative stress is linked to formation of amyloid plaques in AD and subsequent increased neurodegeneration that occurs.[40,41] It is possible that protective effects of DHA may also be due to its ability in reducing inflammation, improving blood flow, and reducing plague aggregation.[36] Moreover, DHA increases glutathione reductase activity, thereby decreasing lipid peroxide and reactive oxygen species levels[17,30] protecting neurons from oxidative assault by free radicals. These reports clearly underline the protective effects of DHA on memory function. Nonetheless, contrasting reports cast a shadow over beneficial effects of DHA in dementia. In fact, a recent publication from CSHA failed to show any protective association between DHA and risk of dementia.[27]

Summary

The increase in prevalence of dementia is a reality. As the life expectancy increases so will the number of patients having AD. Therefore, it is important to identify effective means of countering severe burden of AD on both affected individual and the society as a whole. Of various theories suggested so far, dietary intervention in particular role of omega-3 based fatty acids has attracted significant attention as a possible means of improving memory function in patients with AD or at worst delaying the onset of cognitive impairment and dementia. Although a number of studies have provided a clear indication to the beneficial effects of dietary omega-3 substitutes, this has not been unequivocal. In fact, a significant number of preclinical and clinical trials have failed to show any significant impact of consumption of omega-3 on preserving or improving memory function in demented participants. Therefore, at present, it is not possible to draw a firm conclusion to the role of omega-3 on cognitive function. This clearly indicates the need for larger multicenter clinical trials to address the controversy over the importance of omega-3 substitution in preserving memory function.

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