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A REVIEW ON IMPORTANCE OF DOCOSAHEXAENOIC ACID (DHA) IN ALZHEIMER'S DISEASE

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ABSTRACT

Alzheimer's disease is a devastating disease whose recent increase in incidence rates has broad implications for rising health care costs. In this paper, we review here the published studies examining the possible links between fish and seafood consumption or docosahexaenoic acid (DHA) intake and cognitive impairment, cognitive decline and dementia including Alzheimer's disease (AD). Our assessment showed that the prospective epidemiological studies are most supportive for a protective role of fish and seafood intake against the risk of cognitive decline, all-cause dementia and AD.

INTRODUCTION

Alzheimer's disease (AD) is a progressive degenerative disease that attacks vulnerable brain regions resulting in impaired memory, thinking and behavior and is devastating both to the afflicted person and to that person's family. It is one of the most common form of dementia in the elderly characterized by a progressive loss of memory, deterioration of virtually all intellectual functions, increased apathy, decreased speech function, disorientation, and gait irregularities. AD is caused by changes in the cerebral cortex, basal forebrain, and other areas of the brain. Symptoms of AD are characterized by the build-up of a signature plaque containing an abundance of the protein amyloid-β (Aβ) on the surface of brain neurons and within the cells, leading to nerve cell degeneration. This so called amyloid-beta (Aβ) peptide is derived from a normal transmembrane protein containing about 700 amino-acids called amyloid precursor protein (APP), located in the limbic system as well as other parts of the brain [1]. Aβ peptides promote pro-inflammatory responses and are activators of neurotoxic pathways leading to brain cell dysfunction and cell death. Another type of amyloid in AD is located inside the neurons is the neurofibrillary tangles of hyperphosphorylated tau protein forming paired helical filaments (PHF).

It is estimated that 20–40% of the population now over the age of 85 years may have AD [2]. Numbers are predicted to rapidly increase with the aging of the population in the US and other industrialized countries and to reach an estimated 14 million in the US and 50 million worldwide [3]. Females are slightly more likely than males to develop AD. Individuals with Down's syndrome are more likely to develop AD than the general population. Most of the subjects with mild cognitive deficits will progress to AD at a rate of 10-15% per year compared with healthy control subjects who convert at a rate of 1-2% per year [4,5].

AD attacks every socioeconomic and ethnic group. This common problem of aging will expand in the near future because people are living longer. A positive link has been well established between seafood consumption and cognition. This reduced risk of dementia was thought to be associated with marine long chain omega-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) [6]. Post-humous

examinations have revealed that the brains of persons with AD contain less DHA in the grey matter of the frontal lobe and hippocampus [7]. It has also been consistently established by large population based studies linking fish consumption and / or plasma fatty acids that omega-3 fatty acids retard cognitive decline over time [8].

1. Role of Docosahexaenoic acid (DHA) in Alzheimer's disease

DHA is a 22-carbon carboxylic acid with six *cis*-double bonds, the first being on the third carbon from the omega end, hence the fatty acid nomenclature 22:6, n-3 (**Figure 1**). Other names for DHA include cervonic acid, all-cis-docosa-4,7,10,13,19-hexaenoic acid[9]. With 6 double bonds DHA can be rapidly oxidized by oxygen radical attack, oxidized forms of DHA are enriched in an AD brain [10,11].Oxygen radical attack, not only on lipids but also DNA and protein, occurs early in AD and may play a significant role in AD pathogenesis [12]. Because DHA competes with the n-6 series arachidonic acid for esterification into phospholipids diets are typically judged sufficient in the context of both absolute levels and n-6/n-3 ratios.

DHA is the second most abundant of the omega-3 fatty acids in fish oil, concentrated in brain cells as well as in the photoreceptors of the retina. It has been assumed that the DHA is integrated into the phospholipid membrane of the brain cells thus mainly exerted actions related to normal cell function, *viz.* propagation of electrical signals conducted in the neurons. Patients with AD have reduced levels of DHA [13] but it is not known whether this is due to a seafood-deficient diet or if it is a secondary reaction to an inflammatory process such as free-radical mediated lipid peroxidation. Reduced DHA serum content has even been correlated with general cognitive impairment in people not diagnosed with AD [14]. DHA deficiency from dietary depletion appears to cause cognitive deficits [15, 16,17].

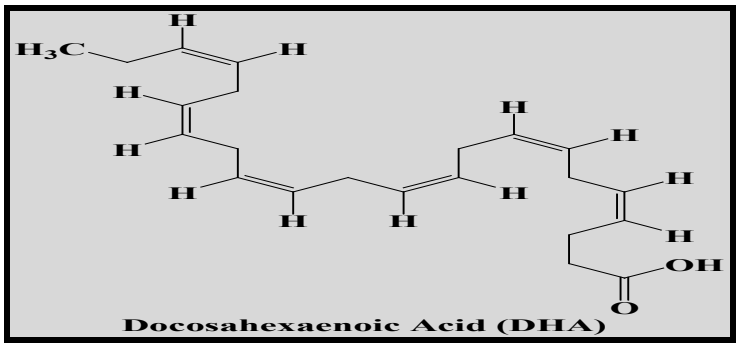

Figure 1: Structure of DHA

DHA was found to be the most prominent fatty acid in the brain, retina, and spermatozoa [18], and is necessary for vision, cognition, and sperm motility. It is found to be rich in the neurons and synaptosomes of the cerebral cortex, where it occupies the no. 2 position of membrane phospholipids. In premature infants whose formula contained DHA balanced with n-6 arachidonic acid, both vocabulary and motor performance has been increased along with improvement in vision [19]. Monkeys deficient in dietary n-3 fatty acids have reduced vision, abnormal electro-retinograms, and greater amounts of stereotypic behavior and polydypsia. DHA can also be synthesized in the body from the n-3 fatty acid α-linolenic acid (18:3), which is present in some vegetable oils and some nuts and seeds. However, this synthetic step is relatively inefficient.

2. Studies Explaining the Role of DHA in AD

Different studies have been performed uptill now. Epidemiologic studies in healthy people have clearly demonstrated that eating fish has a protective effect against development of AD. Cohort studies from Rotterdam, Holland [20], Bordeaux, France [21], and the US [22] have unanimously demonstrated a lower risk of developing dementia in people with a regular intake of seafood compared with non-fish eaters. Recently DTA has been demonstrated to have a neuroprotective effect against brain ischemia in a mouse model [23]. In vitro experiments using retinal pigment epithelial cells demonstrated potent anti-apoptotic as well as anti-inflammatory actions [24]. The compound has therefore been given the name Neuroprotectin, underlining the importance of this fatty acid in the protection of brain cells.

The study named Framingham Heart Study showed that persons with plasma phosphatidylcholine DHA in the top quartile of values had a significantly lower risk (47%) of developing all-cause dementia than did those in the bottom quartile [25]. Significantly (P = 0.04) greater protection was obtained from consuming 2.9 fish meals/week than from consuming 1.3 fish meals /week.

In another study, the investigators estimated the amount of fish in the diet or measured the composition of the plasma fatty acids at baseline, which provided an index of fish

consumption. Cognition was estimated at baseline with follow-up years later to correlate any change in cognition with the baseline fish consumption, plasma fatty acids, or both. In past few years, some studies were found to be positive and some were found to be negative.

The Minneapolis study of 2251 white men and women began in 1987–89 with analyses of plasma fatty acids in cholesterol esters and phospholipids [26]. Three neuropsychological tests were given at baseline and again between 1990 and 1992 and between 1996 and 1998. The risk of decreased global cognition was greater with higher concentrations of palmitic acid and arachidonic acid (20:4n-6) in both cholesterol esters and phospholipids. In contrast, the risk of cognitive decline was lower with a higher concentration of linoleic acid (18:2n-6). Cognitive decline was associated with lower plasma n-3 fatty acids (DHA+EPA) in the subgroup of subjects with hypertension and dyslipidemia, but this association was not found for the entire group.

In another *in-vitro* experiment in human neurons and glial cells, production of Aβ peptides increased as a function of the number of weeks in culture, mimicking the aging procedure of brain cells. However, when DTA was added, a repression of Aβ-triggered activation of proinflammatory and antiapoptotic genes was observed [27]. These results indicated that DTA promoted cell survival via the induction of antiapoptotic and neuroprotective gene-expression programs that suppress Aβ peptide-induced neurotoxicity. In the same study, the production of Aβ peptides was also reduced due to down-regulation of the specific gene.

Two recently published studies have confirmed data from the *in-vitro* studies presented above. One study demonstrated a protective effect of DHA on brain cell death [28]. The other study showed positive effects in the prevention of amyloid formation in the mouse brain [29]. Using a new imaging technique it was possible to demonstrate positive effects in the brain of the group treated with Omacor, in addition to improvement in cognition.

Further three cross-sectional studies investigated the impact of fish and seafood consumption or ω3 PUFA on the risk of cognitive impairment in nondemented subjects (**Table 1**). Only one of them reported that both fish and long-chain ω3 PUFA intakes lowered the risk of cognitive impairment significantly in nondemented middle-aged

adults [31]. In the other two studies involving older participants, neither fish consumption nor ω3 PUFA intakes were associated significantly with lower risk of cognitive impairment [32,33]. Therefore, there is not much support for protection against cognitive impairment by fish and long chain ω3 PUFA intakes when evaluated by a cross-sectional design.

Table 1: A cross-sectional study showing fish or ω3 PUFA intake lowers (A) or does not lower (B) the risk of cognitive impairement in non-demented middle aged and old adults.

Reference	Participants		Exposure[a]		Risk
	N	Age (yrs)	Fish (gm/d)	EPA+DHA (gm/d)	Value
A. Lower Risk					
Kalmijn et al. [31]	1613	45-70	3	0.17	0.8[b]
B. No Risk Reduction					
Kalmijn et al. [32]	476	69-89	≈20	0 to 2	NS
Van Gelder et al. [33]	210	70-89	0 to ≈20	0.02 to 0.4	NS

[a] The fish and ω3 PUFA intakes were derived from food frequency questionnaires or a dietary histories

[b] odds ratio with P = 0.05

DHA: Docosahexaenoic acid; EPA: Eicosapentaenoic acid; PUFA: Polyunsaturated fatty acids; NS: Not significant.

Most support for a protective role of fish and seafood consumption comes from prospective studies investigating their effects against the risk of dementia or AD (**Table2**). Four studies revealed that 1 to 2 servings of fish per week lowered the risk of AD [34-37]. In contrast, estimated ω3 PUFA or ω6 + ω3 PUFA intakes were associated with lower risk of dementia in two of three studies [35, 39], and with no risk reduction of AD in three of four studies [35, 38-40]. Thus, the effects of estimated EPA+DHA or long-chain ω3 PUFA intakes did not consistently match that of fish intake. The lack of a consistent association may well be related to methodological differences such as varying follow-up periods, variability of ω3 PUFA composition among different species of fish consumed, and to other nutrients in fish and seafood such as proteins, iodine and/or selenium, which may interact with ω3 PUFA and assist in lowering the risk for dementia and AD [41]. All

together, we suggest that the available epidemiological literature provides good arguments for the potential of fish and seafood consumption to protect against cognitive impairment, cognitive decline and dementia including AD. However, the effects of the estimated EPA+DHA or long chain ω3 PUFA intakes do not consistently reproduce those obtained by fish and seafood consumption.

Table 2: Prospective studies showing fish or ω3 PUFA intake lowers (A) or does not lower (B) the risk of all-cause dementia (D) or Alzheimer's disease.

Reference	Participants N	Participants Age (Yrs)	Follow-up (Yrs)	Amount fish/wk[a] PUFA gm/d[a] (mean or range)	Risk Value D	Risk Value AD
1. FISH INTAKE						
A. Lower Risk						
Kalmijn et al. 1997	5386	68	2.1	≈130 gm serving	0.4[b]	0.3[b]
Barberger-Gateau et al. 2007	5944	≥65	4	1 serving	0.6[c,†]	0.7[c]
Barberger-Gateau et al. 2002	1416	≥68	7	≥1 serving	0.7[c]	0.7[c]
Huang et al. 2005	1570	≥65	5.4	>2 servings	0.7[c,†]	0.6[c,†]
B. NO RISK REDUCTION						
Morris et al., 2003	815	65-94	3.9	≥1 serving		NS
Huang et al. 2005	474	≥65	5.4	>2 servings	NS[‡]	NS[‡]
Barberger-Gateau et al. 2007	1479	≥65	4	1 serving	NS[‡]	
2. ω3 PUFA INTAKE						
A. LOWER RISK						
Morris et al. 2003	815	65-94	3.9	1.8 g ALA+EPA+DHA 0.06 g DHA		0.3[b]
Laitinen et al. 2006	1449	65-80	21	0.5 - 0.8 g ω6+ω3 0.9 - 2.9 g ω6+ω3	0.4d,[‡] 0.5d,[‡]	NS 0.4[d,‡]
Barberger-Gateau et al. 2007	7783	≥65	4	ω3e	0.4[c]	NS
B. NO RISK REDUCTION						
Engelhart et al. 2002	5395	68	6	16.6 g total ω6 1.3 g total ω3	NS	NS

[a] Derived from food frequency questionnaires or dietary histories

[b] Relative risk

[c] Hazard ratio

[d] Odds ratio

[e] From ω3 rich oils, amount and type of ω3 PUFA not reported

[†] For apolipoprotein E ε4 non-carriers only

[‡] For apolipoprotein E ε4 carriers only

Results are significant at $p \leq 0.05$

ALA: alpha-linolenic acid; DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid; NS: not significant; PUFA: polyunsaturated fatty acids.

In each of these studies, the n-3 fatty acids retarded the decline in cognition over time. One mechanism for the positive effect could be the antithrombotic and anti-inflammatory properties of EPA [42]. Moreover, the entrance of DHA into the brain could correct DHA deficiency in membrane phospholipids in the cerebral cortex in patients with Alzheimer disease [43], and EPA would counter the pro-inflammatory action of arachidonic acid, which is a precursor of cytokine and pro-inflammatory eicosanoids that may be associated with greater cognitive decline. The association of palmitic acid in the plasma cholesterol esters and phospholipids is of interest. This 16 carbon saturate is associated with thrombosis and the elevation of plasma LDL cholesterol that can lead to atherosclerotic obstruction. Both of these conditions could increase the tendency to develop dementia. Alzheimer disease is so prevalent and so disastrous that definitive clinical trials to delay or prevent it must be carried out. In the meantime, because evidence exists that n-3 fatty acids prevent episodes of sudden death, the American Heart Association has already recommended that all adults consume 2 fish meals/week [44]. For people who are allergic to fish or who cannot obtain fish, we suggest the consumption of one fish-oil capsule (1000 mg) per day. The possibility that the fatty acids DHA and EPA in fish and fish oil may delay the ravages of Alzheimer disease is of great interest.

3. Prevention of Alzheimer's disease

There is strong evidence that the incidence and prevalence of AD is affected by diet, with high risk factors found to include alcohol, fat, refined carbohydrates, salt, and total caloric consumption, and preventative factors found to include antioxidants, essential trace minerals, estrogen for post-menopausal women, fish and fish oil, and anti-inflammatory therapeutic agents. In addition, exercise has also been found to reduce the incidence of stroke for men (no corresponding effect was found for women) [45], and also reduces the risk of developing AD. Thus, healthy diets should be considered the first line of defense against the development and progression of AD, as well as all other chronic degenerative diseases. The finding that the highest correlation between diet and AD incidence and prevalence is found 3-5 years before the study period suggests that diet modifications late in life can still affect the risk of developing AD.

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