THE APPLICATION OF OMEGA-3 FATTY ACIDS IN ALZHEIMER’S DISEASE: THE EVIDENCES FROM PLACEBO-CONTROLLED CLINICAL TRIALS

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Summary. The past few decades have been a period of rapid expansion of knowledge of omega-3 polyunsaturated fatty acids (PUFAs). It is well known that the central nervous system is highly enriched in long-chain PUFA of the omega-6 and omega-3 series. These fatty acids are structural components of neuronal membranes and influence the cellular function both directly, through effects on membrane properties, and also by acting as a precursor pool for lipid-derived messengers. This review focuses on the results of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) supplementation in population with Alzheimer’s disease (AD). We screened 83 titles, reviewed 50 studies and found 5 studies that pertained to our objectives. Patients with AD have been shown to be deficient in DHA, and supplementing them with EPA+DHA reverses this deficiency. However, the screened double-blind, placebo-controlled clinical trials confirmed the benefits of supplementation with omega-3 PUFAs only for patients with very mild cognitive impairment.

Key Words: omega-3 PUFAs, Alzheimer’s disease, food supplements, neurology

Introduction

Omega-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), also known as polyunsaturated fatty acids (PUFAs) are long-chain, polyunsaturated fatty acids of plant and marine origin. [1] Because these essential fatty acids cannot be synthesized by the human body, they must be derived from dietary sources such as salmon, tuna, halibut, algae, some plants, nut oils etc.

The past few decades have been a period of rapid expansion of knowledge of omega-3 PUFAs. Clinical evidence is strongest for heart disease and problems that contribute to heart disease, but omega-3 fatty acids may also be used for high blood pressure, diabetes, rheumatoid arthritis, osteoporosis etc. It is well known that the central nervous system is highly enriched in long-chain PUFA of the omega-6 and omega-3 series. These fatty acids are structural components of neuronal membranes and influence the cellular function both directly, through effects on membrane properties, and also by acting as a precursor pool for lipid-derived messengers. [2-4;5]

There is increasing evidence that increased intake of EPA and DHA, may confer benefits in a variety of psychiatric and neurological disorders, especially neurodegenerative conditions.[6] Particularly, DHA is a key component of all cell membranes and is found in abundance in the brain and retina.[7] There is multitude of overlapping mechanisms underlying these beneficial effects. These are related to direct actions on plasma membranes (related to alterations to the biophysical properties of the cell membrane and modulation of phosphatidylserine synthesis), altered inflammatory response and control of gene expression.

In the past 20 years there has been an emerging interest in the application of omega-3 PUFAs in some neurological disorders such as Alzheimer’s disease (AD). Currently, the number of people with AD is estimated to be 26.6 million and it is expected to increase to 106.2 million in less than 40 years. [8] Alzheimer’s disease is the most common cause of dementia in the developed world and from the perspective of the limited availability and efficacy of current treatment options every positive result is worth to be discussed and investigated further.

This review focuses on the results of EPA and DHA supplementation in population with Alzheimer’s disease.
The application of omega-3 fatty acids in Alzheimer’s disease...

Materials and Methods

We screened 83 titles, reviewed 50 studies – of which 45 underwent a detailed review, and found 5 studies that pertained to our objectives. We included controlled clinical trials and excluded open-label trials and case reports. We have included only publications in English language. We have abstracted data on the effects of omega-3 PUFA, on study design, relevant outcome, source, and duration of omega-3 PUFA consumption.

Results

Oxidative stress, inflammation, and increased cholesterol levels are all mechanisms that have been associated with AD pathology. The activation of multiple inflammatory cells in the brain plays a central role in development of AD. Release of IL-1β, IL-6, and TNF α from microglia cells may lead to dysfunction of the neurons in the brain. [9]

Many studies suggest that Alzheimer’s disease is strongly correlated with decreases in omega-3 PUFA levels in the brain and peripheral tissues. Serum cholesterol ester EPA and DHA have been shown to be significantly lower in Alzheimer’s disease (AD) patients than in age-matched controls, and furthermore the decrease in DHA levels correlate with the severity of dementia. Several epidemiologic studies have reported a decreased risk of AD with fish consumption.[6,8] A study found that a diet characterized by higher intakes of omega-3 PUFAs rich foods was strongly associated with a lower AD risk.[10]

Many placebo-controlled clinical trials examined the effect of omega-3 PUFAs supplementation (Table 1).

Table 1. Double-blind, placebo-controlled trials with PUFAs

<table>
<thead>
<tr>
<th>Indication</th>
<th>Clinical trials</th>
<th>Design</th>
<th>N of patients enrolled</th>
<th>Dosage</th>
<th>Results in omega-3 PUFA group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Quinn et al.(2010): 18 months randomized, double-blind placebo-controlled study.[15]</td>
<td>402</td>
<td>1 g DHA/twice daily</td>
<td>DHA was not found to affect either the rate of change on ADAS-cog scores or the CDR sum of boxes compared with placebo.</td>
<td></td>
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<tr>
<td></td>
<td>Chiu et al. (2008): 24-week, randomized, double-blind placebo-controlled study.[13]</td>
<td>23</td>
<td>1.8 g/day or placebo (olive oil)</td>
<td>There was no significant difference in the cognitive portion of the Alzheimer’s Disease Assessment Scale (ADAS-cog) change during follow-up. Omega-3 PUFAs group showed significant improvement in ADAS-cog compared to the placebo group in participants with mild cognitive impairment ($p = 0.03$).</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vedin et al. (2008): double-blind, placebo-controlled, randomized trial. [14]</td>
<td>25, first subjects to be randomized in the Omega AD Study</td>
<td>1.7 g DHA/0.6 g EPA or placebo for 6 months</td>
<td>Decreased levels of IL-1β, IL-6, and granulocyte colony–stimulating factor from peripheral blood mononuclear cells at 6 month.</td>
<td></td>
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<tr>
<td></td>
<td>Freund-Levi et al.(2006): 1 year randomized, double-blind, placebo-controlled clinical trial.[11]</td>
<td>174</td>
<td>1.7 g DHA/0.6 g EPA or placebo for 6 months</td>
<td>A significant ($P&lt;.05$) reduction in MMSE decline rate in a subgroup (n = 32) with very mild cognitive dysfunction (MMSE &gt;27 points), in omega-3 PUFA group.</td>
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Freund-Levi et al. (2006) confirmed that the administration of omega-3 PUFAs in patients with mild to moderate AD did not delay the rate of cognitive decline according to the MMSE or the cognitive portion of the Alzheimer Disease Assessment Scale but a significant (P<0.05) reduction in MMSE decline rate in a subgroup (n = 32) with very mild cognitive dysfunction (MMSE ≥27 points), in omega-3 PUFAs group compared with the placebo group was observed. A similar arrest in decline rate was observed between 6 and 12 months in this placebo subgroup when receiving omega-3 PUFAs.[11]

Unintended weight loss is experienced by many patients with AD, and EPA+DHA supplementation has had a positive effect on weight gain. In a study performed in 2010 by Irving et al. patients’ weight significantly increased by 0.7 kg in omega-3 PUFAs group at 6 month (P = 0.02) and by 1.4 kg at 12 month (P < 0.001) and was observed mainly in patients with a Body Mass Index (BMI) <23 at the start. The study showed that those patients with a lower BMI preferentially gained weight compared with those patients already with a higher BMI.[12]

Chiu et al. (2008) studied the use of omega-3 PUFAs monotherapy in people with cognitive impairment (including 23 participants with mild or moderate Alzheimer’s disease and 23 participants with mild cognitive impairment), receiving 1.8 g omega-3 PUFAs/day or placebo (olive oil). The study confirmed no significant difference in the cognitive portion of the Alzheimer’s Disease Assessment Scale (ADAS-cog) change during follow-up in these two groups. However, the omega-3 PUFAs group showed significant improvement in ADAS-cog compared to the placebo group in participants with mild cognitive impairment (p = 0.03), which was not observed in those with Alzheimer’s disease.[13]

Although many studies have addressed effects of EPA-rich fish oils on inflammatory reactions, few have investigated effects of DHA-rich fish oils on ex vivo cytokine release. In 2008 Vedin et al. observed as a part of OmegAD project that 6 months of treatment with a DHA-rich preparation was associated with clear effects on released cytokines from peripheral blood mononuclear cells (PBMCs) stimulated ex vivo with LPS. A significant decline of released IL-1, IL-6, and G-CSF was noticed. [14]

Quinn et al. (2010) investigated the effect of application of 1 g of DHA twice a day in a patient population with mild to moderate AD.[15] DHA was not found to affect either the rate of change on ADAS-cog scores or the Clinical Dementia Rating (CDR) sum of boxes compared with placebo.

Recent study, performed by Shinto et al. (2014) evaluated the effects of supplementation with omega-3 PUFAs alone or omega-3 PUFAs plus alpha lipoic acid, compared to placebo on oxidative stress biomarkers in AD and have found no beneficial effect of omega-3 PUFAs on the oxidative stress (measured by peripheral F2-isoprostane levels), Alzheimer Disease Assessment Scale-cognitive subscale (ADAS-cog) and Mini-Mental State Examination (MMSE).[16]

Conclusion

Patients with AD have been shown to be deficient in DHA, and supplementing them with EPA+DHA reverses this deficiency. [17-21] However, the screened double-blind, placebo-controlled clinical trials confirmed the benefits of supplementation with omega-3 fatty acids only for patients with very mild cognitive impairment. Due to a small number of studies that met our inclusion criteria, further research is necessary before substantive conclusions can be drawn. Additional research on the effects of omega-3 PUFAs needs to be performed and more double-blind, placebo-controlled clinical trials with a larger size, higher doses and of an adequate length (e.g., 3 years or more) need to be conducted. Some authors suggest that disappointing results from clinical trials examining the effect of omega-3 PUFAs supplementation in AD is due to ineffective targeting of individuals who might benefit from high doses of omega-3 PUFAs, in particular because of their genetic susceptibility to AD.[22]

References


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