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Revisión

Effect of eicosapentaenoic acid and docosahexaenoic acid supplementations to control cognitive decline in dementia and Alzheimer's disease: a systematic review

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Abstract

Introduction: **there is a lack of consensus on the benefits of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) supplementations on cognition in dementia and/or Alzheimer's disease (AD) elderly.**

Objective: **this study presents a systematic review of the results of randomized clinical trials about this topic. The adopted search criteria were randomized clinical trials involving elderly over 65 years of age with no limit to the year of publication of the study.**

Results: **we identified 139 articles, and from the eligible ones a reverse search was conducted. The quality of the trials was assessed using the Jadad scale. Of the four selected studies, three were related to mild to moderate AD elderly, of both genders. Mini Mental State Examination, Alzheimer's Disease Assessment Scale Cognitive, and Clinical Dementia Rate were the main tests used to assess cognitive performance.**

Conclusion: **EPA and/or DHA supplementations did not affect scores obtained on the cognitive tests. However, supplementation with EPA and/or DHA improved verbal fluency and attention in patients who had only very mild dementia or AD or presented *APOE*ε4 negative genotype. In case of advanced AD elderly patients, EPA and/or DHA supplementations did not reduce cognitive decline rates.**

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Key words: *N-3 fatty acids. Dietary supplements. Cognition. Alzheimer disease. Dementia.*

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EFECTO DE LA SUPLEMENTACIÓN DEL ÁCIDO EICOSAPENTAENOICO Y ÁCIDO DOCOSAHEXAENOICO PARA CONTROLAR EL DETERIORO COGNITIVO EN LA DEMENCIA Y ENFERMEDAD DE ALZHEIMER: UNA REVISIÓN SISTEMÁTICA

Resumen

Introducción: **no existe consenso sobre los beneficios de la suplementación con ácido eicosapentaenoico (EPA) y ácido docosahexaenoico (DHA) sobre la cognición de las personas mayores con demencia y/o Alzheimer.**

Objetivo: **esta revisión sistemática muestra los resultados de ensayos clínicos randomizados al respecto.**

Métodos: **se realizó una búsqueda de ensayos clínicos randomizados llevados a cabo en personas mayores de 65 años, sin estabelecer límites en cuanto al año de publicación.**

Resultados: **se identificaron 139 artículos y a partir de los artículos candidatos se llevó a cabo una búsqueda inversa. La calidad de los ensayos clínicos aleatorios se evaluó mediante la escala de Jadad. De los cuatro estudios seleccionados, tres valoraban ancianos, con diagnóstico de enfermedad de Alzheimer de leve a moderada, en ambos sexos. Mini Examen del Estado Mental, Enfermedad de Alzheimer, Escala de Evaluación Cognitiva y Tasa Clínica de Demencia fueron los principales test utilizados para estudiar el rendimiento cognitivo.**

Conclusión: **la suplementación de EPA y/o DHA no afectó las puntuaciones en las pruebas cognitivas. Sin embargo, la suplementación con EPA y/o DHA mejoró la cognición en los dominios de fluidez y de atención verbales en pacientes que únicamente presentaban demencia leve o enfermedad de Alzheimer o el genotipo APOEε4 negativo. En los pacientes ancianos con enfermedad de Alzheimer avanzada, la suplementación con EPA y/o DHA no redujo las tasas de deterioro cognitivo.**

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Palabras clave: *Ácidos grasos n-3. Cognición. Suplementos dietéticos. Enfermedad de Alzheimer. Demencia.*

Introduction

Alzheimer's disease (AD) and other dementias are public health problems that affect approximately 35 million people worldwide. There should be a threefold increase in this number by 2050[1]. It costs about 604 billion dollars/year, and it will increase due to population aging and to the absence of an effective treatment, a fact that recently motivated the G8 to put dementia as a priority in terms of public health priority[2].

The pathogenesis of dementia has been associated with the deposition of β-amyloid plaques and tau protein in the brain[3]. Diet is a modifiable risk factor in the etiology of this disease. Prospective epidemiological studies have identified a lower risk for AD in response to the consumption of food rich in antioxidants and unsaturated fat[4], besides fish[5,6], and fish oil[7] rich in omega-3 fatty acids, especially eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).

In some studies, DHA supplementation reduced the damage caused by the deposition of β-amyloid plaques and tau protein in the brain of transgenic mice carrying the disease mutant gene[8,9]. EPA anti-inflammatory effect also appears to mitigate the effects of aging and of β-amyloid plaques in aged mice[10].

Human epidemiological and intervention studies on the effects of EPA and DHA intakes on dementia are scarce. AD patients show lower concentrations of DHA in the plasma[11], in the temporal lobe, and in the hippocampal brain[12]. DHA supplementation in non-demented elderly appears to reduce cognitive decline[13,14].

Epidemiological studies in humans and experimental studies in animals suggested the positive effects of EPA and DHA supplementation on cognition in dementia and AD elderly patients. However, the results of recently conducted controlled clinical trials in humans have been controversial. Therefore, the purpose of this review study was to analyze some of the published studies on this topic to obtain scientific evidences to identify the effect of supplementation of EPA and DHA on cognitive performance, pointing out some questions that should be explored in future studies.

Methods

Search strategy

The keywords used in the search were docosahexaenoicacid, eicosapentaenoicacid, dementia, Alzheimer's disease and supplementation. We selected PubMed and Science Direct randomized controlled trials, published in English or Spanish, involving elderly over 65 years of age, with no limit for the study year of publication such as. The articles titles and abstracts were analyzed according to the inclusion criteriaFull texts were reviewed to confirm eligibility. From the selected articles, a reverse search of the relevant studies was conducted.

Selection criteria

Randomized clinical trials involving the participation of dementia or AD subjects were selected considering the following criteria: (1) comparing the effect of DHA and/or EPA supplementations (regardless of dose used) versus control; (2) intervention studies lasting at least six months; (3) cognitive assessment as study outcome. All studies were analyzed by two reviewers.

Selected studies quality assessment

Jadad scale[15] was used to evaluate the quality of the randomized controlled trials.

Results

Articles selection

During the initial search, we obtained 139 articles of which 134 were excluded after reading the title and/or summary. The reasons for exclusions were studies out of the theme, non randomized clinical trial, no AD or dementia diagnosis, subjects average age under 65, animal studies, review articles, and ineligible language. After reading in full the five pre-selected articles, one was excluded for not assessing the cognitive aspect as the study outcome. We also tracked the references of selected articles to search for other relevant studies and identified six eligible articles according to the title. After reading the abstracts, we excluded five; four of them did not meet the inclusion criteria and one due to duplicate. Finally, four articles were selected for further analysis and discussion of the results (Figure 1).

Characteristics of studies

Three of the four selected studies involved elderly, of both genders, between 72.6 and 85 years of age on average, and mild to moderate AD diagnosis. Changes in cognitive performance were evaluated using the global scores and/or scores for cognitive domain. The main cognitive tests used were the Mini Mental State Examination[16], Alzheimer's Disease Assessment Scale Cognitive[17], and Clinical Dementia Rate[18] (Table I).

EPA and DHA supplements pills were provided during the day, with doses between 430 and 1,100mg/day of DHA and 150 and 975mg/day of EPA for 6 to 18 months, respectively.

Several researchers[20,21,22] observed positive effects of EPA and/or DHA supplementations in elderly pa-

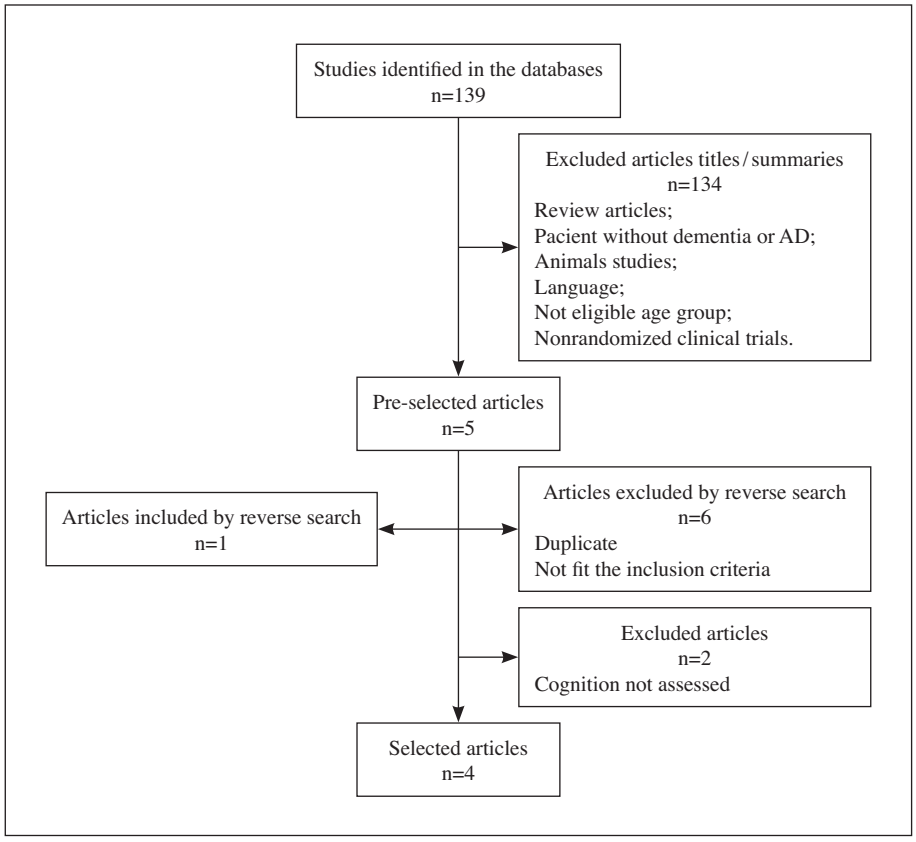

Fig. 1.—Flow chart of study selection.

tients presenting mild to moderate conditions. Patients with dementia only[19], very mild AD[20], and *APOE*ε4 negative genotype[21] showed an improvement on the cognitive tests scores after supplementation.

Quality assessment of the selected studies

The Jadad scores of studies ranged from 1 to 5 points. Half of the studies were considered of good quality (≥3 points) (Table II).

Discussion

The results of this review indicate that most studies failed to demonstrate the beneficial effects of EPA and/or DHA supplementations in reducing cognitive decline in patients with dementia and/or mild to moderate AD. However, supplementation of EPA/DHA in healthy elderly subjects[13] and in those with very mild cognitive impairment[23] it reduced cognitive decline in patients with dementia and AD. Thus, it seems that supplementation is more effective in an earlier stage of the disease. However, the results of the effects of EPA and DHA supplementations in reducing cognitive decline in healthy elderly are controversial.

Healthy elderly, supplemented during 4months with DHA (800mg/day) associated with lutein showed improved cognition, especially in terms of verbal fluency and memory[13]. However, basal plasma concentrations of DHA were not presented in that study limiting further analysis of the obtained results. Supplementation of lower (EPA/DHA = 200mg/500mg for 24 months)[14] and higher daily doses (1,800 mg of EPA-DHA for 26 weeks)[24] did not reduce cognitive decline in healthy elderly. However, these supplementations were not done in combination with antioxidants and fatty acids.

The results of some studies have shown that patients with AD and mild cognitive decline[25] have low plasma concentrations of antioxidants, especially carotenoids[26,27]. Lutein is a predominant carotenoid in human brain tissue[28,29]. Its concentrations seem to be related to cognitive function[28]. Lutein supplementation combined with DHA resulted in better effects in healthy elderly[13]. However, there is insufficient evidence to confirm this benefit.

The assumption that the benefits of EPA and DHA on cognitive decline can lead to beneficial effect when the supplementation of these fatty acids is associated with antioxidants was confirmed after supplementation of EPA and DHA with alpha lipoic acid (ALA). This effect was attributed to the antioxidant property of ALA[22] since no positive effect was observed when subjects received EPA and DHA supplementations only. However, the beneficial effect of ALA has not been confirmed in other studies in which it was used alone or in combination with other antioxidants[30,31]. Due to the possible

Table I
Characteristics of selected studies and their main results

REFERENCE	*n*	*AGE (YEARS), MEAN ± SD*	*GENDER (%)*	*CLINICAL CONDITION*	*COGNITION SCALE*	*CONTROL GROUP*	*TEST GROUP*	*DURATION*	*CONCLUSION*
Terano et al. (1999)[19]	20	85[1]	Both	Mild to moderate dementia	MMSE; HDS-R	No treatment[3]	6 DHA pills/ day (0.72g)	12 months	DHA supplementation improved dementia scores. A positive correlation between DHA serum levels and dementia HDS-R score.
Friend-Levi et al. (2006)[20]	174	72,6±9	F (57) M (43)	Mild to moderate AD	MMSE; ADAS-cog; CDR	4 pills/day (1g each) containing placebo isocaloric oil (1g corn oil, 0.6g including linoleic acid) + 4 mg of vitamin E	4 pills/day (1g each) containing 430mg of DHA and 150mg of EPA + 4 mg of vitamin E	12 months[4]	EPA and DHA did not affect the rate of cognitive decline. However, the very mild cognitive subgroup impairment decreased the rate of decline, the MMSE, compared to placebo. In the placebo group, the supplementation, between 6 and 12 months resulted in a reduction in the rate of cognitive decline by MMSE.
Quinn et al. (2010)[21]	295	76±9.3	M (52.9) F (47.1)	Mild to moderateAD	ADAS-cog; CDR; MMSE	Pills containing soybean oil or corn	2 cpills/day containing from 900 to 1,100mg of extracted algal DHA	18months	EPA and DHA did not affect the rate of cognitive decline. However, in the subgroup with very mild cognitive impairment decreased the rate of decline measured by MMSE compared to placebo. In the placebo group, the supplementation between 6 and 12 months resulted in a reduction in the rate of cognitive decline by MMSE.
Shinto et al. (2014)[22]	39	75,9±8.1	M (61) F (39)	Mild to moderateAD	MMSE; ADAS-cog	3 pills/day of soybean oil with 5% fish oil	3 pills/day of fish oil (675mg/day DHA and 975mg/day EPA)	12 months	The cognitive performance did not differ between the placebo and test groups.

SD: standard deviation; M: male; F: Female; AD: Alzheimer's disease; MMSE: Mini Mental State Examination; HDS-R: Hasegawa's Dementia Rating Scale; DHA: Docosahexaenoic acid; ADAS-cog: Alzheimer's Disease Assessment Scale-Cognitive subscale; EPA: Eicosapentaenoic acid; CDR: Clinical Dementia Rating Scale.
[1]Standard Deviation not informed; [2]Proportion of each gender not informed; [3]The group did not receive placebo; [4]The control group received placebo for only 6 months.

Table II
Quality of the randomized controlled trials included in this review

Jadad Score (Jadad et al., 1996)[15]	*Terano et al. (1999)*[19]	*Freund-Levi et al. (2006)*[20]	*Quinn et al. (2010)*[21]	*Shinto et al. (2014)*[22]
Randomization	1	1	1	1
Randomization of the adequacy	0	0	1	1
Double blinding	0	1	1	1
Blinding Adequacy	0	0	1	1
Description of losses and exclusions	0	1	1	1
Sum of the Jadad score	1	3	5	5
Quality	Low[1]	High[2]	High[2]	High[2]

[1]Low quality = when the sum of the score is less than three; [2]High quality = when the sum of the score is greater than or equal three.

synergistic interaction between EPA/DHA and ALA, more studies are needed to confirm its effectiveness in reducing cognitive decline.

The reduction of oxidative stress by antioxidant vitamins and minerals supplementations is currently being assessed in some studies. However, the use of non-standardized doses and forms of administration hinder conclusions about these benefits, specifically on cognitive impairment[30]. The hypothesis that these substances could improve the benefits of EPA and/or DHA supplementations should be further explored.

Another relevant factor in the investigation of the effects of EPA and/or DHA on dementia cognition is the presence of the allele *APOE*ε4[32]. Epidemiological studies demonstrated that the consumption of omega 3 only by *APOE*ε4 negative genotype subjects reduces the risk of dementia (–28%) and DA (–41%) when fish oil was consumed at least twice a week[7]. In a controlled trial, supplementation of 900 to 1,100mg DHA improved cognition only in *APOE*ε4 negative genotype AD patients[21].

The studies we reviewed used different combinations of behavioral and cognitive tests that allow a more appropriate analysis of cognition. However, in three of these studies[19,20,22] the results were not explored by the cognitive domains of each test applied; only the overall score was achieved. We also observed the lack of standardization of the tools used to assess the cognitive performance, which may limit the comparison of the results obtained in the studies.ADAS-cog[17] and MMSE[16] are instruments that assess the intellectual conditions of patients with suspected dementia, which are able to detect reduction in cognitive decline. On the other hand, CDR is a scale used to determine the severity of dementia[18].

Conclusion

The results of the studies presented showed that mild to moderate supplementation of EPA (ranging from 430 to 900 mg/day) and/or DHA (ranging from 150 to 975mg/day) did not reduce cognitive decline in elderly patients. Some beneficial effects were detected in elderly in the early stage of dementia or AD presenting *APOE*ε4 negative genotype, specifically in the areas of verbal fluency and attention.

The effects of EPA and DHA supplementations alone or in combination with antioxidants on cognitive function should be further explored in controlled studies involving dementia elderly patients.

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