

Association of Omega-3 Fatty Acid and Epileptic Seizure in Epileptic Patients: A Systematic Review

Abstract

The evidence on the association between omega-3 consumption and epileptic seizure is inconsistent. Therefore, we have conducted this systematic review to clarify the possible relationship. Original articles were searched in electronic databases (PubMed, Scopus, Google Scholar, Cochrane, and Ovid) and by reviewing the reference lists of retrieved articles. The main evaluated outcome was the epileptic seizures. We included the English language studies that reported the original data on the effect of omega-3 on epileptic human patients. We included the nine articles with 230 patients in the present systematic review. The mean \pm standard deviation age of them was about 31.01 ± 14.99 years. The average of study duration was 22 ± 15.27 weeks. Omega-3 fatty acid supplements were defined as the sum of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) (1100 mg/d); as the sum of EPA, DHA, and alpha-linolenic acid (5 g/d); and as the sum of EPA alone (565 mg/d) in different studies. Among the nine studies, four studies reported a significant positive association between omega-3 fatty acids and epileptic seizures. However, power and quality of these studies are low, and we cannot consider the beneficial effect of omega-3 on seizures. In addition, five studies did not reveal any significant effect. Majority of the included studies did not show a significant association between omega-3 and epileptic seizure in epileptic patients, but further studies are necessary. It is controversial whether omega-3 fatty acids can produce positive effects on epileptic patients or not.

Keywords: Docosahexaenoic acid, eicosapentaenoic acid, epilepsy, omega-3

Introduction

Epilepsy is the brain disorder and a common neurological disorder that develops by recurrent seizures.^[1-6] It affects the people of all ages, but it is prevalent in the people who are younger than 20 years and people over the age of 60 years.^[7] Its prevalence in developing countries is higher than that of the developed ones.^[5,6] In general, this affects 70 million people worldwide.^[8]

Lately, nonpharmacological treatment of epilepsy and the role of omega-3 fatty acids were investigated.^[9] Omega-3 fatty acids receive from diet or supplements and is necessary for normal brain growth and process.^[10-13] The main part of omega-3 fatty acids in the brain structure is docosahexaenoic acid (DHA) that is composed of 10%–20% of total fatty acids. Alpha-linolenic acid (ALA) and eicosapentaenoic acid (EPA) form <1% of them.^[14] Studies indicated that the level of omega-3 fatty acids in patients with epilepsy decreased remarkably.^[15] ALA is the main

cause of neurological disorders including unusual points in the myelin, nerve endings, and endoplasmic reticulum.^[16]

Some studies reported that omega-3 fatty acid supplementation could suppress the epileptic seizures while the others did not confirm. Animal studies reported that omega-3 fatty acids could elevate the seizure.^[9] Others shown that omega-3 could play a role as an inhibitor of messenger-regulated protein kinase^[13] and had neuroprotective roles.^[17] DHA derivatives such as neuroprotectin D1 (NPD1) have protective role in various inflammatory reactions such as epilepsy,^[18] inhibit cell death, and suppress the cytokines.^[19] In addition, it may decrease the synthesis of energetic radicals and ameliorate the mitochondrial function.^[20-24] In addition, it may affect the seizures through decreasing the cleavage of brain membrane phospholipids and increase them.^[9] It has been proposed that omega-3 fatty acids can modulate calcium and sodium channels and reduce the neuron membrane stimulation.^[25,26] However,

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because of inconsistent results and disagreement of articles in this field, we need a comprehensive study.

The purpose of this systematic review is to summarize the available information and clarify the relationship between omega-3 fatty acid supplementation and epileptic seizure in epileptic patients.

Methods

Search strategy and study selection

We searched PubMed, Scopus, Ovid, Google Scholars and Cochrane up to May 2015 using the following Medical Subject Headings and keywords without restrictions of publication date: (“Epilepsy” OR “seizures” OR “convulsion” OR “seizure*”) AND (“Fatty Acids, Omega-3” OR “Eicosapentaenoic Acid” OR “Fish Oils” OR “alpha-Linolenic Acid” OR “Fatty Acids” OR “Fatty Acids, Unsaturated” OR “Fatty Acids, Essential” OR “Docosahexaenoic Acids” OR “N-3 fatty acid” OR “ALA” OR “DHA” OR “EPA” OR “Linolenic acid” OR “PUFA” OR “Marine omega-3 fatty acids” OR “E-EPA” OR “Long chain fatty acids” OR “Ethyl eicosapentaenoic acid”).

After primary search and removing the duplicate articles, two researchers checked the title and abstracts of all articles. Relevant articles were checked by full text. Excluded studies and vague ones were reviewed by the third researcher. Furthermore, the reference lists from the detected articles were reviewed to distinguish additional relevant studies. Finally, nine articles were selected and assessed in the present study. The selection process for studies is shown in Figure 1.

The present systematic review was performed based on the Preferred Reporting Item For Systematic reviews and Meta-analysis statement recommendation and has been registered by PROSPERO (ID = CRD42015020389).

Inclusion and exclusion criteria

We included English language studies without any time restriction that reported original data on the effect of omega-3 on epileptic seizure in epileptic patients.

Studies were excluded if they fall under the following criteria:

- Animal studies
- Studies that investigate $n = 3$ fatty acid biomarkers on epilepsy
- Those used the drugs besides omega-3
- Review studies
- Studies without our outcomes
- Studies in which omega-3 was an ingredient of supplement.

Data extraction

The included studies were summarized by two independent researchers. We extracted the first author’s last name,

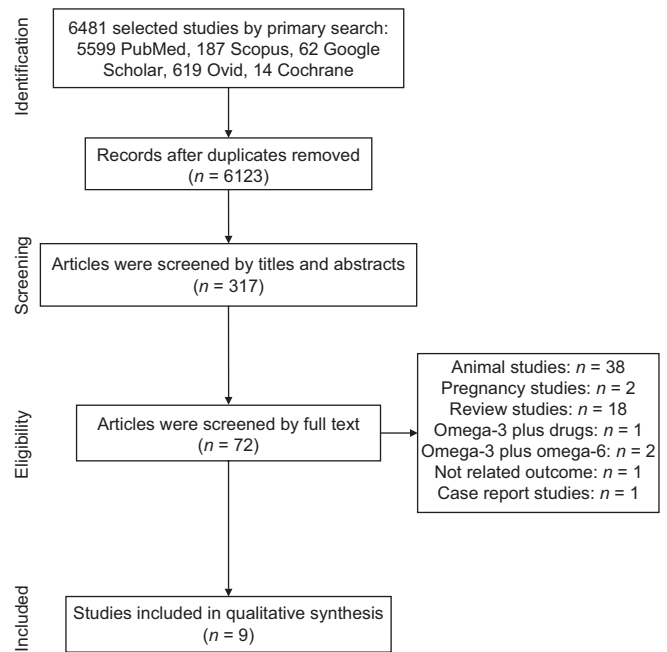


Figure 1: The selection process for studies

publication year, study subjects and demographic traits, study design, study size, type, and dosage of omega-3 fatty acids, and duration of the study [Table 1]. We compared the outcomes between omega-3 intervention group and the control group if available. For one study that reported low- and high-dose, we compared them with placebo group.^[27] Disagreements on data extraction were examined by the third researcher.

Quality assessment

Two investigators assessed the quality of included studies using the Jadad criteria. This score includes 5 points (5 is the highest quality). This allocated 2 points for randomization (1 point for the mention of randomization and the other for the appropriate randomization method). This criteria deduct 1 point if the method of randomization is not appropriate, 2 points for blinding (one point for the mention of blinding and the other for the appropriate method of blinding and 1 point if the method of blinding is not appropriate), and 1 point for the subject’s fate. It means that if the patients do not complete the study, they are eliminated and the reason is explained.

Results

In brief, the titles of 6481 articles were reviewed. Then, 317 of them were checked by titles and abstracts, and 72 full-text papers were screened. Finally, nine articles (eight clinical trials and one cohort study) met the inclusion criteria. Characteristics of the included studies are shown in Table 1.

The seven clinical trial articles were published between 2002 and 2015 that included 205 patients with epilepsy.

Table 1: Summary of included studies about the effect of omega-3 fatty acid on epileptic seizure in epileptic patients

Author (year)	Patients and gender	Age range (years) and mean age	RCT	Diet type (name and composition)		Duration (weeks)	Outcome (mean±SD and n)		Final result	Jadad score
				Intervention	Control		Intervention	Control		
Schlanger et al., 2002 ^[32]	n=5 Female: 4 Male: 1	12-26	-	n=3 PUFA supplement 5 g (DHA, EPA, ALA)	-	24	-	Anticonvulsive drugs	Omega-3 supplement alleviate the seizure	0
Yuen et al., 2005 ^[9]	n=57 Male: 35 Female: 22 Omega: 13 male/ 17 female Control: 22 male/ 5 female	Omega-3: 19-65 Mean: 39 Control: 20-63 Mean: 38	Double-blind, placebo-controlled, parallel group trial	Capsules containing 1000 mg of fish oils (with 171 mg EPA and 112 mg DHA, and <100 IU Vitamin A and <40 IU Vitamin D)	Placebo capsules containing mixed oils (palm olein 70%, rapeseed oil 15%, sunflower oil 15%)	12	n=30 5/29 had 50% reduction in seizures in the first 6 weeks (P=0.051) different: 17% (1.5%-36%) No different in the second 6 weeks (P=0.087)	Antiepileptic drugs	Omega-3 supplements decreased the seizures in the first 6 weeks	3
Puri et al., 2007 ^[30]	n=7 Male: 2 Female: 5 Omega: 3 female/ 0 male Control: 2 female/ 2 male	Omega: 50.7±13.6 Control: 40.5±12.0	Double-blind placebo-controlled trial	Capsules containing 1000 mg fish oil (with 171 mg EPA, 112 mg DHA, <100 IU Vitamin A and <40 IU Vitamin D) Three capsules taken twice daily	Capsules containing mixed oils (palm olein 70%, rapeseed oil 15%, sunflower oil 15%)	12	n=4 percentage PDE: Increase by an average of 0.92±2.34% (P=0.061) n=3 percentage PDE: Decrease by an average of 3.75±2.81% (SD 2.81) γNTP: Increased by an average of 1.73±2.41% (SD 2.41) BBC: Increased by an average of 13.56±7.74% (SD 7.74)	-	No significant correlations between seizure changes and changes in any of the spectroscopic resonances measured	3
Bromfield et al., 2008 ^[31]	n=21 Male: 9 Female: 12 Omega: 5 male/ 7 female Control: 4 male/ 5 female	Omega: 25-55 Mean: 36 Control: 22-62 Mean: 38	Randomized double-blind placebo-controlled trial	Begun at 1.1 g/day (1 week) and then increased to 1.1 g capsules twice daily (EPA plus DHA, 2.2 mg/day in a 3:2 ratio)	Capsules containing mineral oil	4	Decreased to 12% on placebo (P=0.21) QOL, QOLIE-31 overall scores decreased by an average of 6 points (P=0.23)	Antiepileptic drugs, open-label PUFA administration: 19 volunteers, 15 of 19 experienced fewer seizures than baseline, 5 by at least 50% (P=0.02)	Omega-3 has no convincing evidence in reducing the seizures	4

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Table 1: Contd

Author (year)	Patients and gender	Age range (years) and mean age	RCT	Diet type (name and composition)		Duration (weeks)	Outcome (mean±SD and n)		Any other intervention (from)	Final result	Jadad score
				Intervention	Control		Intervention	Control			
DeGiorgio et al., 2008 ^[29]	n=11	18-65	Exploratory, randomized, double-blind, two-period crossover trial 6-week washout period	Fish oil capsules	Soybean	30	Seizure frequency: Increase +11±13% (P=0.051)	Seizure frequency: increase +14±13% (P=0.051)	Antiepileptic drugs	Omega-3 has no effect on seizures	3
				Each capsule : 1200 mg fish oil (216 mg EPA +144 mg DHA)	Oil capsules/ Eight capsules/day		Seizure severity: Reduce - -12±9% (P=0.618)	Seizure severity: decrease - -19±9% (P=0.618)			
Yuen et al., 2012 ^[33]	n=10 Male: 5 Female: 5	23-75	Nonrandomized open trial	Capsules: 500 mg of EPA, and 10 mg mixed tocopherols (no DHA)	-	12	Median seizure frequency: 15 at baseline and 11 during treatment (P=0.26)	-	Antiepileptic drugs	EPA has no effect on seizures	0
				Two capsules a day			Seizure severity reduced in one patient				
DeGiorgio et al., 2015 ^[27]	n=24 Male: 8 Female: 16	18-56 Mean: 33±10.33	Prospective, randomized, three-period crossover clinical trial, twice 6-week washout period	Fish oil capsule: 216 mg EPA and 144 mg DHA (360 mg [r=3] fatty acids per capsule)	Placebo: Three corn oil capsules twice a day	42	Seizure frequency Low: 12.18±2.72	Seizure frequency: 18.34±4.28	Antiepileptic drugs	Low-dose fish oil was effective in reducing seizures	4
				Low-dose group: 1080 mg/day (three fish oil capsules per day)	High-dose group: 2160 mg/day (three fish oil capsules twice a day)		Change from placebo: -33.6% (P=0.02)	Low: 31% reduction in seizure frequency (P=0.05)			

Contd...

Table 1: Contd

Author (year)	Patients and gender	Age range (years) and mean age	RCT	Diet type (name and composition)	Duration (weeks)	Intervention	Control	Outcome (mean±SD and n)	Any other intervention (from)	Final result	Jadad score
Reda et al., 2015 ^[34]	n=70	Range: 4-12 Mean age of intervention group: 6.9±2.5 Mean age of control group: 6.6±2.4	Single-blinded, randomized clinical trial	Intervention: 3-mL daily dose of 1200 mg fish oil providing 240 mg DHA and 360 mg EPA + Vitamin E Control: 3 mL of corn oil daily	12	Seizure frequency: percentage of children having zero attacks per month increased from 0% to 57.1% (P=0.0)	Seizure frequency: Percentage of children having zero attacks per month was 2.9% (P=0.92)	Seizure severity: Median score of the NHS3 was 13 at baseline and decreased to 10 (P=0.44)	Antiepileptic drugs	Omega-3 PUFAs elevated the seizure threshold	3
Dahlin et al., 2007 ^{[28]*}	n=25 Female: 13 Male: 12	Range: 1.5-18.1 Mean: 6.3±4.2	Open prospective cohort	Meat+1 to 2 g fish oil 4 times a day	48 Follow up: After 3, 6, and 12 months	No correlation with seizure response	-	Seizure severity: Median score of the NHS3 was 12 at baseline and remained 10% (P=0.99)	Antiepileptic drugs	No correlation was found between omega-3 and seizures	5

*To assess the quality of Dahlin et al's. study, the Newcastle score was used. PUFA=Polyunsaturated fatty acids, DHA=Docosahexaenoic acid, EPA=Eicosapentaenoic acid, ALA=Alpha-linolenic acid, PDE=Phosphodiester, BBC=Broadband component, γNTP=Gamma-nucleotide triphosphate, SD=Standard deviation, QOLIE=Quality of life in epilepsy form, NHS3=National Hospital Seizure Severity Scale, RCT=Randomized controlled trial

About 52.3% of them were female and 49.3% were male. The mean age was about 31.01 ± 14.99 years. Among these articles, five studies investigated the effect of fish oil^[9,27-30] and two studies assessed fish oil plus Vitamin A and Vitamin D.^[9,30] Omega-3 fatty acid supplements were defined as the sum of DHA and EPA (1100 mg/d),^[31] as the sum of EPA, DHA, and ALA (5 g/d),^[32] and as the sum of EPA alone (565 mg/d)^[33] in different studies. In one study, fish oil was used for intervention group (240 mg DHA and 360 mg EPA plus Vitamin E) and corn oil for control group.^[34]

The average of study duration was 22 weeks. Design of two studies was crossover with washout duration. Two studies investigated meal enriched with omega-3,^[28,32] and the others investigated supplement therapy.^[9,27,29-31,33,34] In a cohort study, the participants received multivitamins plus carnitine. In addition, they received a meal with certain recipe for 1 month and then added fish oil to it.

DeGiorgio *et al.*^[27] investigated low- (1080 mg/d) and high-dose (2160 mg/d) fish oil on epileptic patients with the mean age of 33 ± 10.33 years for 42 weeks. Nearly 25% of participants in low-dose fish oil group indicated a 50% reduction in epileptic seizure frequency as well as 15% of patients in high-dose fish oil group indicated 50% reduction in epileptic seizure compared with placebo. Almost 10% of participants were seizure free with low-dose fish oil during the intervention. In addition, no association was found between fish oil and seizure severity score.

Schlanger *et al.*^[32] have shown that bread enrichment with omega-3 supplement (5 g) contained 46% DHA, 18% EPA, and 1% ALA, and 100 IU Vitamin E could alleviate the seizures in epileptic patients with the mean age of 19 years for 24 weeks. However, they assessed only five patients with no control group and a Jadad score of 0. This cannot be clearly interpreted as a proof of positive effect.

Yuen *et al.*^[9] assessed the effect of fish oil on seizures during 12 weeks of intervention. They reported that patients (with the mean age of 39 years in intervention group and 38 years in placebo group) who took capsules containing 1000 mg of fish oils (with 171 mg EPA and 112 mg DHA and <100 IU Vitamin A and <40 IU Vitamin D) experienced less seizures during the first 6 weeks. However, this reduction was not consistent for the second 6 weeks.

Bromfield *et al.*^[31] investigated epileptic patients with a mean age of 36 years in omega-3 group and patients with a mean age of 38 years in placebo group for 4 weeks. They showed that the patients in the intervention group (polyunsaturated fatty acid [PUFA] supplement: EPA plus DHA, 2.2 mg/day in a 3:2 ratio) did not experience the reduction in seizure. The median seizure frequency was increased to 6% in PUFA and decreased to 12% in placebo group ($P = 0.21$). Overall, there is no remarkable evidence in this field.

In a 30-week crossover study,^[29] patients (mean age of 41.5 years) received eight capsules contain 1200 mg fish oil per day (216 mg EPA + 144 mg DHA). Hence, they received totally 2880 mg of omega-3 fatty acids/day. Findings showed that seizure frequency increased to 11% in intervention group and 14% in placebo group ($P = 0.051$). Hence, no reduction was found in seizure frequency. Seizure severity was measured by the National Hospital Seizure Severity Scale. The mean score decreased from 8.55 at baseline to 7.55 in fish oil group and from 8 to 7.57 during the placebo time. However, this reduction was not significant.

Yuen *et al.*^[33] assessed the effect of EPA (1000 mg of EPA and 20 mg mixed tocopherols) on epileptic patients with a mean age of 49 years for 12 weeks. The median of seizure frequency decreased from 15 to 11, but it was not statistically significant ($P = 0.26$). Thus, they could not show a significant relationship between consumption of EPA supplement and seizure frequency.

Patients in a study of Puri *et al.*^[30] received three capsules contain 1000 mg fish oil (with 171 mg EPA, 112 mg DHA, <100 IU Vitamin A and <40 IU Vitamin D) twice a day for 12 weeks. The mean age of patients in intervention and placebo group was 50.7 ± 13.6 years and 40.5 ± 12.0 years, respectively. The results showed that omega-3 supplementation might relate to decrease of membrane phospholipid separation in patients' brain and metabolism of brain energy development and membrane phospholipid enhancement. However, it was not statistically significant. For this purpose, they reported some biochemical changes such as decrease in phosphodiester percentage (by an average of 3.75 ± 2.81), increase in gamma-nucleotide triphosphate percentage (by an average of 1.73 ± 2.41), and increase in the broadband component (BBC) percentage (by an average of 13.56 ± 7.74) to evaluate the brain changes that might be associated with epilepsy. Finally, there was no correlation between epileptic seizures and biochemical changes.

Dahlin *et al.*^[28] investigated a meal recipe plus fluid fish oil (1–2 g, 4 times a day) in 25 children with a mean age of 6.3 ± 4.2 for 12 months. Sixteen of 25 children after 3 months, 15 of 24 ones after 6 months, and 12 of 19 children after 12 months experienced >50% reduction in seizures. Serum level of EPA and linoleic acid increased, arachidonic acid (AA) decreased and DHA increased insignificantly. However, no correlation was found between change in serum fatty acids and seizure response.

Reda *et al.*^[34] used 3-mL daily dose of 1200 mg fish oil that provides 240 mg DHA and 360 mg EPA plus Vitamin E for intervention group and 3 mL of corn oil daily for control group in their study. The mean age of the participants in intervention group was 6.9 ± 2.5 years and 6.6 ± 2.4 years in control group. After 12 weeks, seizure frequency and severity decreased significantly in intervention group.

Considering the minimal efficacy of supplementation in the placebo group, it seems that omega-3 PUFAs increased the seizure threshold in epileptic patients and may control achieving seizure.

Discussion

This is the first systematic review that assessed the relationship between omega-3 supplementation and epileptic seizures. The results of the studies reported an inconsistent effect of omega-3 fatty acids on epileptic seizures.

Among the nine studies, four of them suggested a significant positive relationship between omega-3 fatty acids and epileptic seizures.^[9,27,32,34] However, power and quality of these study are low, and we cannot consider the beneficial effect of omega-3 on seizures. In addition, five of them did not reveal any significant effect.^[28-31,33]

DeGiorgio *et al.*^[27] claimed that low-dose fish oil was a safe and low-cost method for the reduction of seizures and attenuation of cardiovascular health in people with epilepsy. Schlanger *et al.*^[32] illustrated the mechanism by neuroprotection role, or changes in AA concentrations. EPA inhibits the AA metabolism by affecting the substrate for cyclooxygenase and lipoxygenase enzymes. However, studies that reported positive effect of W_3 on seizures noted the time of seizures per month manually, this manner may cause information bias. In addition, the small sample size and short duration of intervention cannot obtain the decisive results.

Among the studies that did not demonstrate any relationship, Puri *et al.*^[30] used brain spectrum resonances and BBC for between-group comparisons of seizure changes, which can increase the reliability of the results and the design of the study. Another study applied the National Hospital Seizure Severity Scale for seizure assessment; moreover, the duration and crossover design of the study were considered as the positive points for the mentioned study. By the way, this study did not show the significant effects of omega-3 on seizure frequency and severity that high dosage of omega-3 can be the cause of it.^[29] An open-label PUFA trial was designed after one randomized double-blind study and the participants completed the Quality of Life in Epilepsy form to assess the overall health. However, they found no convincing effects of omega-3 on seizures.^[31] Yuen *et al.*, in 2012,^[33] conducted one study on EPA supplementation and found that it has no effect on seizures. One cohort study with sufficient follow-up period found no correlation between omega-3 and seizures.^[28]

The effect of omega-3 on epileptic seizures was determined in animal studies, but it is controversial in humans.^[35] According to previous studies, there are two different pathways regarding the effect of omega-3 on epileptic seizure. The first mechanism is that DHA regulated glutamate transporters (GLTs) such as GLT1,

glutamate aspartate transporter, and excitatory amino acid transporter 1. It seems that in epileptic patients the transporters deregulated, and glutamate was accumulated through the seizures. Besides, NPD1 is a DHA derivate that carries out the protective bioactivity in CNS. It is proposed that NPD1 may increase anti-apoptotic proteins and reduce the pro-apoptotic ones. As well as, the modulating effect of astrocytes and cytokines that were the main participants in epilepsy may be downregulated by NPD1.^[36] Another recommended mechanism is the anti-inflammatory effect of omega-3, through the reduction of pro-inflammatory markers such as C-reactive protein or tumor necrosis factor alpha and increments of the anti-inflammatory agents such as interleukin 10 and transforming growth factor-alpha.

As strength, this is the first systematic review on omega-3 and epileptic seizure. However, some limitations also exist: nonadjustment of energy in most of the trials, inclusion of nonrandomized or nondouble-blind trial, uncontrolled health status, drug abuse, alcohol, and other potential factors in most trials that cause heterogeneity within the results.

Conclusions

Majority of the included studies did not show significant association between omega-3 and epileptic seizure in epileptic patients. However, further studies are necessary. Hence, a few papers reported the certain effect, it is controversial whether omega-3 fatty acids can produce positive effects in epileptic patients or not. Hence, we require more comprehensive data, with large sample size and long follow-up period to clarify the effects and determine the mechanisms.

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Conflicts of interest

There are no conflicts of interest.

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