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Efficacy of DHA and EPA on Serum Triglyceride Levels of Healthy Participants: Systematic Review

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Abstract

Background

Docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) are categorized as omega-3 poly unsaturated fatty acids (PUFAs) that are present in fish oil, etc. DHA and EPA omega-3 PUFAs have a well-established fasting serum triglycerides (TG) lowering effect that may result in normal lipidemia in hyperlipidemic patients. In general, omega-3 PUFAs, such as DHA and EPA, can be ingested easily, and because they are highly safe, they are assumed to be suitable for controlling fasting serum TG in the serum of those who do not require drug treatment. To the best of our knowledge, however, almost all systematic reviews on the effects of omega-3 PUFAs on lowering fasting serum TG are directed at patients fulfilling the diagnostic criteria of dyslipidemia.

Objectives

To review and confirm the preventive effect of omega-3 PUFAs against hypertriglyceridemia or the effect on nondrug treatment in patients with a mild disease, a systematic review was conducted to determine whether there was a fasting serum TG-lowering effect in subjects without disease and those with a slightly higher triglyceride level who consumed DHA and/or EPA orally compared to those with placebo or no intake of DHA and/or EPA.

Search Methods

We evaluated articles from searches of PubMed (1946-February 2016), Ichushi-Web (1977-February 2016), and J Dream III (JST Plus, 1981-February 2016; JMED Plus, 1981-February 2016). The keywords were set as follows: "DHA" or "docosahexaenoic acid" or "EPA" or "eicosapentaenoic acid" and "TG" or "triglyceride" or "triglycerol" or "triacylglycerol" or "neutral lipid.". In addition to the literature group obtained by the database search, we included participants not suffering from any disease (i.e., excluding mild hypertriglyceridemia).

Eligibility Criteria

Before the test selection process, the following inclusion criteria were defined. Participants were healthy men and women including those with mild hypertriglyceridemia (fasting serum TG level, 150-199 mg/dL [1.69-2.25 mmol/L)). Intervention was defined as orally ingested DHA and/or EPA. Comparison was made to placebo intake or no intake of DHA and/or EPA. Results were measured for the fasting serum TG level. The test design was RCT, and quasi-RCT.

Data Abstraction

Various characteristics were extracted from original reports using a standardized data extraction form, including the author of the study, research year, research design, subject characteristics (sex, age, sample size), period, dose of DHA and/or EPA (mg/day), and comparison group.

Main Results

We identified 37 documents for review. Among the 37 reports used to integrate literature results, 25 revealed a decrease in fasting serum TG level due to the oral ingestion of DHA and/or EPA. Sixteen studies on subjects without disease and 21 on subjects with slightly higher fasting serum TG levels were separated and stratified analysis was conducted. Ten of the 16 (normal TG participant) and 15 of the 21 studies (slightly higher TG participant) respectively, indicated that at least 133 mg/day of DHA and/or EPA intervention provided a statistically significant decrease in the fasting serum TG level between an intervention group versus a placebo group.

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Introduction

Cardiovascular disease (CVD) is the leading cause of death worldwide and acts as a major barrier to sustainable human development. To address this major global health concern, in 2011, the United Nations officially recognized several noncommunicable diseases, including CVD, and set up an ambitious plan to dramatically reduce the impact of these diseases in all areas [1].

Hypertriglyceridemia is a type of dyslipidemia characterized by an elevated serum triglycerides (TG] level and has been reported by several prospective studies and randomized controlled trials (RCTs) to be a risk factor for CVD. An increased level of circulating TG is an independent risk factor for the onset of CVD. Hokanson and Austin reported that a fasting serum TG level of 88 mg/dL or more increases the risk of CVD development by 14% and 37% in men and women, respectively [2]. Therefore, lowering or maintaining a low level of fasting serum TG level reduces the risk of CVD.

Fatty acids are comprised of lipids, which are present in almost all parts of the human body. Fatty acids are divided broadly into two categories, saturated and unsaturated fatty acids. Unsaturated fatty acids are further classified into two categories: monounsaturated and poly unsaturated fatty acids (PUFAs). The PUFAs are further divided into two categories: the omega-3 series (metabolic cascade starts with α-linoleic acid (ALA)) and omega-6 series (metabolic cascade starts with linoleic acid (LA)). Docosahexaenoic acid (DHA) and Eicosapentaenoic acid (EPA) are categorized as omega-3 fatty acids [3].

Certain fatty acids, such as ALA and LA, cannot be synthesized in humans, and thus must be obtained in the diet. ALA, a type of omega-3 fatty acid, is converted into DHA and EPA in the body. DHA and EPA also exist naturally in some foods. LA, which is a type of omega-6 fatty acid, is converted to arachidonic acid (AA). DHA and EPA are derived from ALA by a similar biochemical pathway as AA. Omega-3 fatty acids generally lower fasting serum TG levels and very low-density lipoprotein (VLDL) levels in serum among hyperlipidemic patients.

In regard to low-density lipoprotein (LDL) level, omega-3 fatty acids increase it or had no influence among the subjects.

EPA is a carbon number 20, omega-3 PUFA with five double bonds, also abbreviated as 20:5 omega-3. Since it has five cis-type double bonds, the molecule is not a linear structure; hence, its melting point is low and it is easily oxidized. It is almost odorless just after purification, but it undergoes auto-oxidation quickly in air and begins to smell. Peroxide is also unstable, and the volatile component is comprised mainly of the carbonyl compound of the secondary product due to the polymerization and decomposition that causes a fishy odor. It is widely distributed as a major constituent of the fatty acids in marine organisms, such as fish, mollusks, crustaceans, seaweed, and microorganisms. In particular, various sardines, mackerels, saury, and so forth which are blue-backed fish.

DHA is also a PUFA and has 22 carbon atoms and six double bonds, and is abbreviated as 22:6 omega-3. It is the final metabolite of omega-3 PUFA, with the first double bond on the third carbon counted from the methyl group end and starting from ALA (18:3 omega-3). Since it has six cis double bonds, it has a large curved molecular structure; hence, the melting point of a DHA-containing lipid is low, such as is the case for EPA. Moreover, it is extremely easy to oxidize, and readily generates a fishy odor that is mainly composed of a carbonyl compound. DHA is present in various marine animals and microorganisms, including fish, crustaceans, mollusks, microorganisms, etc. Fish with high DHA content include sardines, sauries, skipjack tunas, amberjacks, tunas, and mackerel, and in particular, DHA is present in squid liver oil and fat near the eyeballs of tuna.

In recent years, it has become clear that DHA and EPA have various physiological activities. DHA is the major PUFA present in the brain and is important for brain development and function. The synapses contain abundant DHA, suggesting that DHA is involved in neuron signaling. DHA also is required for the production of a group of compounds called resolvin, which are involved in the body's reaction to inflammation in the brain. Resolvin synthesized specifically from DHA and EPA helps to relieve inflammation caused by ischemic stroke (reduction of blood flow). EPA also suppresses the production of inflammatory compounds, such as cytokines and alleviates inflammatory reactions.

Omega-6 fatty acids account for more than 10 times the omega-3 fatty acids in most American meals. At present, there is well-known scientific agreement that omega-3 fatty acids intake should be increased and omega-6 fatty acid intake should be decreased to promote health; however, it is unknown whether the desired ratio of omega-6 and omega-3 fatty acids exists in meals, and how much omega-6 fatty acid ingestion is necessary to inhibit omega-3 production when large amounts of omega-6 are ingested.

Researchers at the Tufts Educational Policy Committee reviewed the database of the Third National Health and Nutrition Examination Survey (NHANES III; 1988–1994) and investigated the intake of omega-3 fatty acids in the United States. ALA intake was significantly lower in males than in females, and greater in adults than in children. It became clear that there were fewer subjects with CVD than without a history of CVD. Only 25% of the population ingested DHA and EPA in a given day. The average daily intake was 14 g for LA, 1.33 g for ALA, 0.04 g for EPA, and 0.07 g for DHA.

ALA is present in green leafy yellow vegetables, nuts, vegetable oils (such as canola and soybean oils), and especially linseed or linseed oil. Good sources of DHA and EPA include seafoods (fish, crustaceans, mollusks, seaweeds and their oils and fish eggs). LA is present in several foods consumed by Americans, such as meat and vegetable oils (safflowers, sunflowers, corns, soybeans, and so forth), as well as processed foods using these oils. Daily consumption of ALA recommended by the Institute of Medicine was set at 1.1–1.6 g and LA at 11–17 g for adults, but the daily adequate intake of DHA and EPA were not set [4].

Omega-3 PUFAs have a well-established fasting serum TG lowering effect that may result in normal lipidemia in hyperlipidemic patients [5-13]. In general, omega-3 PUFAs, such as DHA and EPA, can be ingested easily, and because they are highly safe, they are assumed to be suitable for controlling fasting serum TG in the serum of those who do not require drug

treatment. To the best of our knowledge, however, almost all systematic reviews on the effects of omega-3 PUFAs on lowering fasting serum TG are directed at patients fulfilling the diagnostic criteria of dyslipidemia. Therefore, our aim was to review and confirm the preventive effect of omega-3 PUFAs against hypertriglyceridemia or positive effects for nondrug treatment in patients with a mild disease. A systematic review was conducted to determine whether there was a fasting serum TG-lowering effect in subjects without disease and those with a slightly higher TG level who consumed DHA and/or EPA orally compared to those with placebo or no intake of DHA and/or EPA.

Method

Identification of Relevant Research

PubMed (1946–February 2016), Ichushi-Web (1977–February 2016), and J Dream III (JSTPlus, 1981–February 2016; JMEDPlus, 1981–February 2016) were independently searched by two reviewers (Y. C, and Y. T). The keywords were set as follows: "DHA" or "docosahexaenoic acid" or "EPA" or "eicosapentaenoic acid" and "TG" or "triglyceride" or "triglycerol" or "triacylglycerol" or "neutral lipid.". In addition to the literature group obtained by the database search, we included participants without any disease (i.e., excluding mild hypertriglyceridemia). Our systematic literature search utilized Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Eligibility Criteria

The following inclusion criteria were defined prior to the test selection process:

Participants were healthy adult men and women including those with mild hypertriglyceridemia (fasting serum TG level, 150–199 mg/dL (1.69–2.25 mmol/L)). [2] Intervention was defined as orally ingested DHA and/or EPA. [3] A comparison was made for placebo intake or no intake of DHA and/or EPA. [4] Results were measured according to the fasting serum TG level. [5] The test design was RCT, and quasi-RCT. Based on these requirements, two reviewers (Y. T and H. M) independently selected studies and extracted data regarding the study characteristics and outcomes from the selected studies.

Data Abstraction

Various characteristics were extracted from original reports using a standardized data extraction form, including author of the study, research year, research design, subject characteristics (sex, age, sample size), period, dose of DHA and/or EPA (mg/day), and comparison group.

Risk of Bias Assessment

Using the Cochrane Collaboration tool to evaluate the risk of bias[42]; low, ambiguous, or highly biased risks for five categories (random sequence generation, assignment hiding, blinded participants and personnel, incomplete outcome data, and selective outcome report) were evaluated in each study. Quality assessments for each included study were also conducted using the Cochrane Collaboration's tool for assessing risk of bias. Disagreements at any step were resolved through discussion.

Result

We found 812 reports from the database retrieval, collections, and other cited references. A total of 53 duplicated studies were excluded. We selected 193 of 759 reports that were at the primary (title and summary) screening stage. Finally, 37 reports meeting the eligibility criteria were extracted at second (full text) screening stage. Figure 1 summarizes the selection process steps. Characteristics of the 37 documents selected are listed in Table 1 together with bibliographic information. Fasting serum TG levels of control and intervention groups of the 37 reports are listed in Table 2 [5-41]. For the total risk of bias, both studies were assessed as having an "overall low risk of bias" (data not show).

Among the 37 reports used to qualitatively the results, 25 revealed a decrease in fasting serum TG level due to oral ingestion of DHA and/or EPA. Sixteen studies on subjects without disease and 21 on subjects with slightly higher fasting serum TG levels were separated and subjected to stratified analysis. Ten of the 16 (normal TG participant) and 15 of the 21 studies (slightly higher TG participant), respectively, intake of an at least 133 mg/day of DHA and/or EPA intervention revealed a statistically significant decrease in the fasting serum TG level between the intervention group and

Table 1. Characteristics of the selected 37 documents.

No.	Author	Reference	PICO	Participants	Dose	Study term
54	Burns-Whitmore B, et al.	Nutr J, 13: 29 (2014)	P：healthy adult male and female I：DHA / EPA C：placebo O：TG level, Cardiovascular risk	[Placebo group] [Intervention group] N=20, 38±3 years old	DHA 429 mg, EPA 34 mg	8 weeks
74	O'Sullivan A, et al.	J Nutr, 144(2): 123–131 (2013)	P：healthy adult male and female I：DHA/EPA C：placebo O：TG level, lipid metabolism	[Placebo group] N=42, 34.1±12.0 years old [Intervention group] ・HR group N=28, 37.2±12.0 years old ・LR group N=13, 38.0±9.6 years old	DHA 1,000 mg, EPA 2,000 mg	6 weeks
138	Signori C, et al.	Eur J Clin Nutr, 66(8): 878–884 (2012)	P：healthy adult female I：DHA/EPA, etc. C：no intervention O：Breast cancer risk, lipid-profile including TG level	[Placebo group] N=8, 35-75 years old [Intervention group] N=11, 35-75 years old	DHA 1,500 mg, EPA 1,860 mg	12 months
165	García-Alonso FJ, et al.	Eur J Nutr, 51 (4): 415–424 (2012)	P：healthy adult female I：DHA / EPA C：placebo O：TG level, lipid metabolism	[Placebo group] N=7, 35-55 years old [Intervention group] N=11, 35-55 years old	DHA 125 mg, EPA 125 mg	2 weeks
172	Bragt MCE, et al.	Nutr Metab Cardiovasc Dis, 22(11): 966–973 (2012)	P：adult male and female I：DHA/EPA C：placebo O：TG level, lipid metabolism	[Placebo group] [Intervention group] N=20, 52±12 years old	DHA 1,200 mg, EPA 1,700 mg	6 weeks
181	Ulven SM, et al.	Lipids, 46(1): 37–46 (2011)	P：healthy adult male and female I：DHA/EPA C：no intervention O：TG level, lipid metabolism	[Placebo group] N=42, 40.5±12.1 years old [Intervention group] ・FO group N=43, 38.7±11.1 years old ・KO group N=44, 40.3±14.8 years old	・FO group DHA 414 mg, EPA 450 mg ・KO group DHA 195 mg, EPA 348 mg	7 weeks

188	Mann NJ, et al.	Lipids, 45(8): 669–681 (2010)	P：healthy adult male and female I：DHA/EPA C：placebo O：TG level, lipid metabolism	[Placebo group] N=7, 29±5 years old [Intervention group] ・FO group N=10, 30±8 years old ・SO group N=10, 31±6 years old	・FO group DHA 810 mg, EPA 210 mg ・SO group DHA 450 mg, EPA 340 mg	14 days
225	Watanabe N, et al.	Int J Food Sci Nutr, 60 (S5): 136–142 (2009)	P：healthy adult male I：DHA / EPA C：placebo O：TG level, lipid metabolism	[Placebo group] [Intervention group] N=17, 50.1±9.2 years old	DHA 540 mg, EPA 1,260 mg	4 weeks
236	Caslake MJ, et al.	Am J Clin Nutr, 88(3): 618–629 (2008)	P：healthy adult male and female I：DHA/EPA C：placebo O：TG level, lipid metabolism	[Placebo group] [Intervention group] N=312, 45.0±0.7 years old	・LD group DHA 407 mg, EPA 293 mg ・HD group DHA 1,047 mg, EPA 753 mg	8 weeks
245	Buckley JD, et al.	J Sci Med Sport, 12(4): 503–507 (2009)	P：adult male I：DHA/EPA C：placebo O：TG level, lipid metabolism	[Placebo group] N=13, 23.2±1.1 years old [Intervention group] N=12, 21.7±1.0 years old	DHA 1,560 mg, EPA 360 mg	5 weeks
248	Gunnarsdottir I, et al.	Int J Obes (Lond), 32(7): 1105–1112 (2008)	P：healthy adult male and female I：DHA / EPA C：placebo O：TG level, lipid metabolism	[Placebo group] N=76, 32.1±5.3 years old [Intervention group] ・CD group N=79, 31.3±5.7 years old ・SD group N=80, 31.3±5.3 years old ・FO group N=79, 31.0±5.3 years old	・CD group DHA 207 mg, EPA 54 mg ・SD group DHA 1,370 mg, EPA 774 mg ・FO group DHA 430 mg, EPA 633 mg	8 weeks
257	Plat J, et al.	J Nutr, 137 (12): 2635–2640 (2007)	P：healthy adult male I：DHA/EPA C：placebo O：TG level, lipid metabolism	[Placebo group] [Intervention group] N=11, 59±9 years old	DHA 500 mg, EPA 600 mg	6 weeks
262	Kobayashi K, et al.	Asia Pac J Clin Nutr, 16(3): 429–434 (2007)	P：healthy adult male and female I：DHA/EPA C：placebo O：TG level	[Placebo group] N=18, 48.4±7.7 years old [Intervention group] N=20, 48.5±7.8 years old	DHA 280 mg, EPA 660 mg	8 weeks

282	Bovet P, et al.	Nutr Metab Cardiovasc Dis, 17(4): 280–287 (2007)	P：healthy adult male and female I：DHA/ EPA C：placebo O：TG level, lipid metab-olism	[Placebo group] [Intervention group] N=25, 34.8±7.9 years old	DHA 124 mg, EPA 9 mg	3 weeks
305	Wu WH, et al.	Eur J Clin Nutr, 60(3): 386–392 (2006)	P：adult female I：DHA C：placebo O：TG level, lipid metab-olism	[Placebo group] N=11, 52.3±5.1 years old [Intervention group] N=1452.6±4.4 years old	DHA 2,140 mg	6 weeks
325	Buckley R, et al.	Br J Nutr, 92 (3): 477–483 (2004)	P：healthy adult male and female I：DHA/EPA C：placebo O：TG level, lipid metab-olism	[Placebo group] N=15, 48±4 years old [Intervention group] ・EH group N=15, 46±3 years old ・DH group N=12, 45±4 years old	・EH group DHA 729 mg, EPA 4,752 mg ・DH group DHA 4,914 mg, EPA 846 mg	4 weeks
334	Theobald HE, et al.	Am J Clin Nutr, 79(4): 558–563 (2004)	P：healthy adult male and female I：DHA/EPA C：placebo O：TG level, lipid metab-olism	[Placebo group] [Intervention group] N=38, 40-65 years old	DHA 680 mg	3 months
419	Grimsgaard S, et al.	Am J Clin Nutr, 66(3): 649–659 (1997)	P：healthy adult male and female I：DHA/EPA C：placebo O：TG level, lipid metab-olism	[Placebo group] N=77, 45±6years old [Intervention group] ・EH group N=75, 44±5years old ・DH group N=72, 43±5years old	・EH group DHA 48 mg, EPA 3,764 mg ・DH group DHA 3,556 mg, EPA 72 mg	7 weeks
420	Lovegrove JA, et al.	Br J Nutr, 78 (2): 223–236 (1997)	P：healthy adult male I：DHA/EPA C：placebo O：TG level, lipid metab-olism	[Placebo group] [Intervention group] N=9, 50±7.2 years old	DHA 500 mg, EPA 860 mg	22days
421	Harris WS, et al.	Am J Clin Nutr, 66(2): 254–260 (1997)	P：healthy adult male and female etc. I：DHA/EPA C：placebo O：TG level, lipid metab-olism	[Placebo group] [Intervention group] N=20, 31±9years old	DHA 1,145 mg, EPA 2,055 mg	3 weeks

433	Conquer JA, et al.	J Nutr, 126 (12): 3032–3039 (1996)	P：healthy adult male and female I：DHA C：placebo O：TG level, lipid metabolism	[Placebo group] N=12, 29.6±1.7 years old [Intervention group] N=12, 29.6±1.7 years old	DHA 1,620 mg	6 weeks
434	Ågren JJ, et al.	Eur J Clin Nutr, 50(11): 765–771 (1996)	P：healthy adult male I：DHA / EPA C：no intervention O：TG level, lipid metabolism	[Placebo group] N=14, 23±2 years old [Intervention group] ・FD group N=13, 23±2 years old ・FO group N=14, 23±2 years old ・DH group N=14, 24±4 years old	・FD group DHA 670 mg, EPA 380 mg ・FO group DHA 952 mg, EPA 1,328 mg ・DH group DHA 1,680 mg	14 weeks
435	Hamazaki T, et al.	J Nutr, 126 (11): 2784–2789 (1996)	P：healthy adult male and female I：DHA / EPA C：placebo O：TG level, lipid metabolism	[Placebo group] N=17, 21-30 years old [Intervention group] N=18,21-30 years old	DHA 1,775 mg, EPA 241 mg	13 weeks
468	Hansen JB, et al.	Eur J Clin Nutr, 47(7): 497–507 (1993)	P：healthy adult male I：DHA/EPA C：placebo O：TG level, lipid metabolism	[Placebo group] N=10, 21-47 years old [Intervention group] ・TG group N=11, 21-47 years old ・EE group N=10, 21-47 years old	TG group DHA 1,400 mg, EPA 2,200 mg ・EE group DHA 1,200 mg, EPA 2,200 mg	7 weeks
490	Luley C, et al.	Arzneimittelforschung, 42(1): 77–80 (1992)	P：healthy adult male and female I：DHA/EPA C：no intervention O：lipid-profile including TG level	[Placebo group] [Intervention group] ・Study DI N=16, 21-55 years old	DHA 1,440 mg, EPA 2,040 mg	4 weeks
			P：healthy adult male and female I：DHA/EPA C：no intervention O：lipid-profile including TG level	[Placebo group] [Intervention group] ・Study D Ⅲ N=15, 21-55 years old	DHA 4,320 mg, EPA 6,120 mg	4 weeks

505	Childs MT, et al.	Am J Clin Nutr, 52(4): 632–639 (1990)	P：healthy adult male I：DHA/EPA C：placebo O：lipid-profile including TG level	[Placebo group] [Intervention group] N=8, 29±2 years old	・PO group DHA 681 mg, EPA 2,560 mg ・TU group DHA 4,514 mg, EPA 1,568 mg ・SA group DHA 1,380 mg, EPA 1,104 mg	3 weeks
510	Blonk MC, et al.	Am J Clin Nutr, 52(1): 120 –127 (1990)	P：healthy adult male I：DHA / EPA C：no intervention O：lipid-profile including TG level	[Placebo group] N=10, 33.7±6.2 years old [Intervention group] ・LD group N=11, 33.7±6.2 years old ・MD group N=10, 33.7±6.2 years old ・HD group N=14, 33.7±6.2 years old	・LD group DHA 600 mg, EPA 900 mg ・MD group DHA 1,200 mg, EPA 1,800 mg ・HD group DHA 2,400 mg, EPA 3,600 mg	12 weeks
529	Zucker ML, et al.	Atherosclero-sis, 73(1): 13–22 (1988)	P：healthy adult male and female, et al I：DHA/EPA C：placebo O：lipid-profile including TG level	[Placebo group] [Intervention group] N=9, 36-60 years old	DHA 2,160 mg, EPA 3,240 mg	6 weeks
567	Fujimoto, et al.	Journal of Japa-nese society of Clinical Nutri-tioomega-33(3): 120–135 (2011)	P：adult male and female I：DHA/EPA C：placebo O：TG level	[Placebo group] N=52, 47.9±9.2 years old [Intervention group] N=49, 46.1±10.1 years old	DHA 260 mg, EPA 600 mg	12 weeks
583	Tamai,et al.	Pharmacology and Therap, 36 (4): 333–345 (2008)	P：adult male and female I：DHA / EPA C：placebo O：TG level	[Placebo group] N=36, 49.8±9.0 years old [Intervention group] N=39, 48.9±8.9 years old	DHA 910 mg, EPA 200 mg	12 weeks

707	Dyerberg J, et al.	Eur J Clin Nutr, 58(7): 1062–1070 (2004)	P：healthy adult male I：DHA/EPA, et al C：placebo O：risk for Cardiovas-cular related including TG level	[Placebo group] N=27, 37.6±10.6 years old [Intervention group] N=24, 39.2±10.5 years old	DHA 949 mg, EPA 1,492 mg	8 weeks
709	Prisco D, et al.	Thromb Res, 76 (3): 237–244 (1994)	P：healthy adult male I：DHA/EPA C：placebo O：lipid-profile includ-ing TG level	[Placebo group] N=10, 32±4y ears old [Intervention group] N=10, 32±4 years old	DHA 1,400 mg, EPA 2,040 mg	4months
712	Rizza S, et al.	Atherosclerosis, 206(2): 569–574 (2009)	P：healthy adult male and female I：DHA/EPA C：placebo O：lipid-profile includ-ing TG level	[Placebo group] N=24, 29.9±6.2 years old [Intervention group] N=26, 29.9±6.2 years old	DHA/EPA 1,700 mg	12 weeks
715	Logan SL, et al.	Plos One, 10 (12): e0144828 (2015)	P：healthy adult female I：DHA/EPA C：placebo O：lipid-profile includ-ing TG level	[Placebo group] N=12, 66±1years old [Intervention group] N=12, 66±1 years old	DHA 1,000 mg, EPA 2,000 mg	12 weeks
755	Matsumoto	Pharmacology and Therapy, 44 (2): 235–246 (2016)	P：healthy adult male and female I：DHA/EPA C：placebo O：TG level	[Placebo group] N=26, 59.1±5.3 years old [Intervention group] N=28, 57.4±5.8 years old	DHA 544 mg, EPA 59.2 mg	12 weeks
757	Rajkumar H, et al.	Mediators In-flamm, Article ID 348959 (2014)	P：healthy adult male and female I：DHA/EPA, et al. C：placebo O：lipid-profile includ-ing TG level.	[Placebo group] N=15, 40-60 years old [Intervention group] N=15, 40-60 years old	DHA 120 mg, EPA 180 mg	6 weeks
758	Marckmann P, et al.	Arterioscler Thromb Vasc Biol, 17(12): 3384–3391 (1997)	P：healthy adult male I：DHA/EPA C：placebo O：lipid-related includ-ing TG level.	[Placebo group] N=24, 41±9 years old [Intervention group] N=23, 41±9 years old	DHA 508 mg, EPA 355 mg	4 weeks

Table 2. Triglyceride level of control and intervention groups of 37 study documents.

No.	Intervention group （pre）		Intervention group（post）	Intervention group（mean difference）	Intervention group vs. placebo group (mean difference）	Vs. baseline （p value）	Between groups （p value）
54	1.13 (1.07_1.18)		0.97 (0.87_1.08)	NA	NA	NA	NS
74	HR group	81.7±58	58.1±35	NA	NA	NA	<0.05
	LR group	84.6±32	73.1±26	NA	NA	NA	NS
138	119±15.1		101±14.0	NA	NA	<0.05	NS
165	65.91±8.51		65.45±7.93	NA	NA	NS	NS
172	1.63±0.59		NA	NA	−0.34	NA	0.048
181	FO group	0.95±0.541	0.94±0.542	−0.01±0.462	NA	NS	NS
	KO group	1.10±0.638	1.01±0.649	−0.09±0.417	NA	NS	NS
188	FO group	1.25±0.65	0.99±0.45	−0.26	NA	NS	NS
	SO group	1.58±0.52	1.18±0.37	−0.40	NA	<0.05	NS
225	98.3±52.4		106.7±70.9	NA	NA	NS	NS
236	LD group	1.25±0.04	1.17±0.03	NA	NA	NA	<0.017
	HD group	1.28±0.04	1.13±0.03	NA	NA	NA	<0.017
245	1.14±0.13		NA	−0.32±0.09	NA	NA	<0.001
248	CD group	1.31±0.73	NA	−0.28±0.51	NA	NA	0.038
	SD group	1.18±0.52	NA	−0.26±0.44	NA	NA	0.001
	FO group	1.15±0.73	NA	−0.20±0.61	NA	NA	0.035
257	1.53±0.60		1.11±0.47	NA	NA	NA	NS
262	4 weeks	1.05±0.63	0.91±0.34	NA	NA	NA	NS
	8 weeks		0.88±0.34	NA	NA	NA	<0.05
282	GA group	0.68±0.23	0.54±0.15	NA	NA	0.013	NA
	GB group	0.68±0.42	0.61±0.25	NA	NA	NS	NA
	（total）	0.68	0.57	（−15.6%）	（−18.3%）	<0.01	<0.01
305	1.40±0.62		1.16±0.46	−0.25±0.59	NA	NA	NS
325	EH group	1.18±0.19	0.92±0.15	NA	NA	0.003	NS
	DH group	1.16±0.19	0.72±0.07	NA	NA	0.006	0.032
334	1.03±0.094		1.01±0.089	NA	−0.18 (−0.37_0.05)	NS	NS

419	EH group		1.23±0.57	NA	−0.15±0.40	NA	<0.01	0.0001
	DH group		1.24±0.58	NA	−0.22±0.31	NA	<0.001	0.0001
420	1.54±0.54			1.49±0.37	NA	NA	NS	NS
421	1.44±0.34			1.05±0.29	NA	NA	NA	<0.001
433	3 weeks		0.96±0.11	0.75±0.09	NA	NA	<0.05	NS
	6 weeks			0.80±0.11	NA	NA	<0.05	NS
434	FD group	4 weeks	1.36±0.47	1.27±0.45	NA	NA	NS	NS
		9 weeks		0.99±0.31	NA	NA	<0.05	<0.05
		14 weeks		1.16±0.40	NA	NA	<0.05	<0.05
	FO group	4 weeks	1.21±0.35	1.11±0.24	NA	NA	NS	NS
		9 weeks		0.95±0.18	NA	NA	<0.05	NS
		14 weeks		0.89±0.13	NA	NA	<0.05	<0.05
	DH group	4 weeks	1.17±0.38	1.03±0.27	NA	NA	NS	NS
		9 weeks		1.00±0.33	NA	NA	<0.05	NS
		14 weeks		0.97±0.21	NA	NA	<0.05	<0.05
435	0.82±0.55			0.81±0.58	−0.01±0.34	NA	NS	NS
468	TG group		0.83±0.13	NA	−0.19±0.09	NA	NA	NS
	EE group		0.82±0.14	NA	−0.05±0.10	NA	NA	NS
490	D I		NA	NA	NA	−15 (−52_3)	NA	0.0008
	DⅢ		NA	NA	NA	−34 (−55_−4)	NA	0.0008
505	PO group		NA	NA	NA	(−34%±6%)	NA	<0.01
	TU group		NA	NA	NA	(−44%±7%)	NA	<0.05
	SA group		NA	NA	NA	(−45%±10%)	NA	NS
510	LD group		1.01±0.14	0.87±0.12	NA	NA	NA	<0.05
	MD group		0.93±0.07	0.70±0.07	NA	NA	NA	<0.05
	HD group		1.00±0.09	0.78±0.06	NA	NA	NA	<0.05
529	0.87±0.07		0.87±0.07	0.67±0.05	NA	NA	NS	NS
567	NA		NA	NA	−24.1	NA	NA	<0.05

583	4 weeks	172±6	140±9	NA	NA	<0.05	NS
	8 weeks		120±8	NA	NA	<0.05	<0.05
	10 weeks		126±10	NA	NA	<0.05	NS
	12 weeks		129±7	NA	NA	<0.05	<0.05
707	1.34±0.11		0.99±0.07	NA	NA	NA	<0.05
709	2 months	1.2±0.3	0.9±0.1	NA	NA	NS	NA
	4 months		0.9±0.2	NA	NA	NS	NA
712	116.8±72.6		86.2±43.6	−30.6±40.0	NA	<0.01	<0.01
715	1.30±0.14		1.01±0.14	NA	NA	<0.05	NS
755	4 weeks	140.5±11.0	133.7±12.6	−6.8±8.8	NA	NA	NS
	8 weeks		132.0±8.8	−8.5±9.6	NA	NA	0.028
	12 weeks		132.8±10.0	−7.8±6.8	NA	NA	0.040
757	105.90±6.53		102.62±6.44	NA	NA	<0.05	NS
758	1.06±0.09		0.93±0.09	NA	NA	<0.01	NS

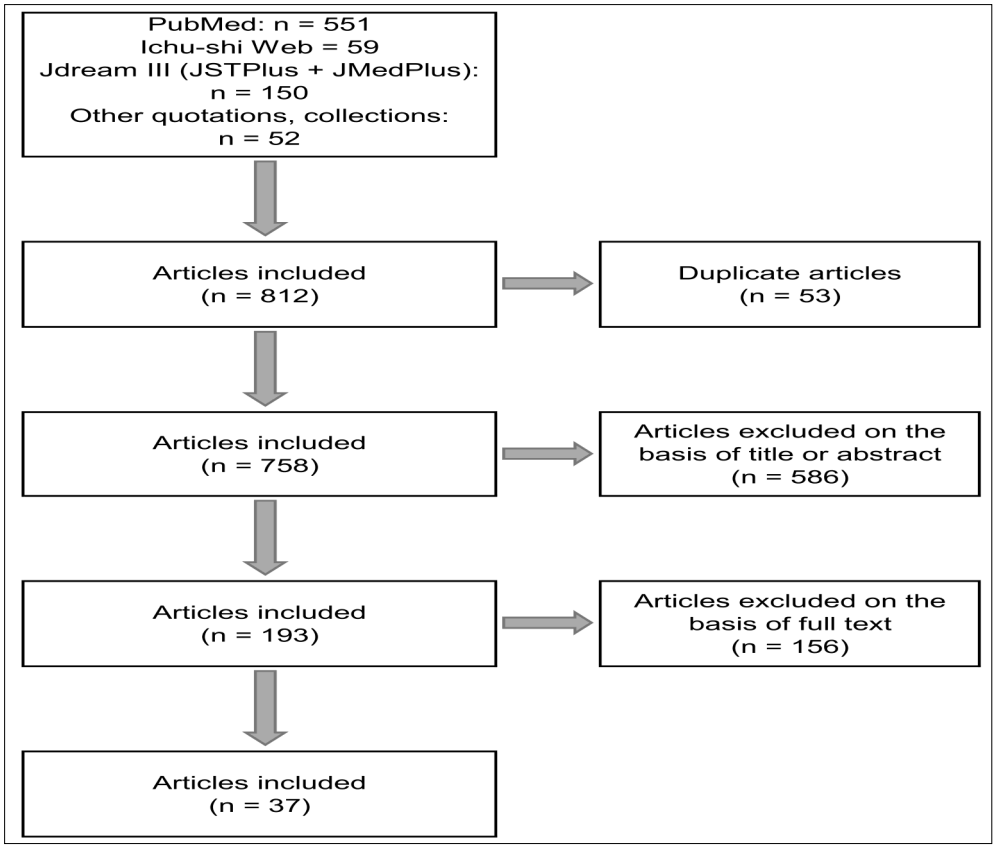

Figure 1. Flow diagram of study selection process.

placebo group. Clinical trials were conducted around the world, and subjects varied in terms of age, sex and race. Moreover, there were several methods for ingesting DHA and/or EPA in foods. Due to the clinical heterogeneity, the results were not quantitatively integrated, but qualitatively integrated and evaluated. Regardless of the diversity of these subjects and the type of intake, there were lower fasting serum TG levels. In this study, DHA and/or EPA intake ranged from 133–10,440 mg and fasting serum TG levels lowered during a 2-week to 12-month DHA and/or EPA oral intake period. Furthermore, there was no evidence of harmful effects due to the intake of DHA and/or EPA.

Discussion

The aim of this study was to confirm the preventive effect of DHA and/or EPA on hypertriglyceridemia or the effect on nondrug treatment for people with a slightly higher fasting serum TG level. A systematic review examined whether oral DHA and/or EPA compared to placebo or no DHA and/or EPA would lower serum TG levels in participants without disease and for those with a slightly higher fasting serum TG level. Among the 37 RCTs, there were 16 healthy subjects and the remaining 21 subjects had slightly higher fasting serum TG levels. Among the former 16 RCTs, significant differences were found in the five double-blind RCTs with a high evidence level, and four studies suggested a lowering effect, although there were no significant differences. Considering that a ceiling effect exists for healthy subjects, this result might suggest the magnitude of the preventive effect of DHA and/or EPA. Among the 21 RCTs targeting people with somewhat higher fasting serum TG levels, several reported reduced fasting serum TG levels after oral ingestion of DHA and/or EPA, suggesting that oral intake of DHA and/or EPA suppresses the progression to hypertriglyceridemia. Thus, DHA and/or EPA dietary intake could contribute to decreasing the number of persons who require medicine to control their fasting serum TG level.

Although several previous studies have reported the fasting serum TG lowering effect of DHA and/or EPA in subjects with hyperlipidemia, our study strongly suggests that the effect is maintained among the subjects with borderline hyperlipidemia and normal lipidemia. Overall, the studies involving dietary interventions assessed in our review revealed that consuming 133–10,440 mg of DHA and EPA produces fasting serum TG lowering effects in healthy or slightly higher fasting serum TG level individuals.

EPA is already used as an ethical drug, and thus, its effect can be considered to be well established; however, the mechanism of omega-3 fatty acids, such as DHA and EPA, to lower the fasting serum TG level, remains unclear. There are some hypothetical mechanisms, including inhibition of diacylglycerol acyltransferase, increase in plasma lipoprotein lipase activity, decrease in liver lipid production, and increase in liver beta oxidation [43].

Based on the results of the preclinical and clinical trials, omega-3 fatty acids have been proposed as exerting a decreasing action on fasting serum TG via numerous mechanisms. For example, it is believed to reduce lipid production in the liver by suppressing the expression of sterol regulatory element binding protein-1c. This is due to the downregulation of expression of cholesterol, fatty acids, and TG synthase [44, 45]. It also is presumed to increase beta-oxidation of fatty acids, and consequently, the TG are suppressed by decreasing the substrate necessary for the synthesis of TG [46]. Furthermore, omega-3 fatty acids are assumed to inhibit TG synthesis in the liver by inhibiting important enzymes involved in hepatic TG synthesis, such as phosphatidic acid phosphatase and diacylglycerol acyltransferase [47]. Moreover, it has been reported to increase the removal of fasting serum TG from circulating VLDL and chylomicron particles [48, 49].

DHA and EPA, the major omega-3 fatty acids, have been reported to lower fasting serum TG levels; however, they are known to have different effects on LDL and high density lipoprotein (HDL) [50-52]. In a direct comparative study, in a meta-analysis comparing the effects of DHA and EPA, DHA was associated with a greater decrease in fasting serum TG and a greater increase in LDL than EPA. DHA also increased HDL compared to placebo, but EPA did not [51]. Further studies are needed to clarify the mechanisms and significance of these differences [50-52].

Research on most omega-3 fatty acids is directed toward DHA and EPA; however, recently omega-3 docosapentaenoic acid (DPA) also has been drawing attention. The level of DPA in serum has is individually associated with a reduction in the risk of myocardial infarction and coronary heart disease [53,54]. When the DPA level in the serum decreases, the risk of peripheral arterial disease such as vascular plaque formation increases [55, 56]. DPA has a stronger inhibitory action on platelet aggregation than DHA and EPA [57]. Like DHA and EPA, DPA has been reported to decrease the expression of inflammatory genes [58]. As the fasting serum TG-lowering mechanism of action of long-chain omega-3 fatty acids differs from that of other lipid-lowering drugs, such as statins, they can potentially provide complementary benefits on the lipid profile when administered in combination [35]. This is supported by a study examining the synergistic effect of the lowering action of fasting serum TG by omega-3 fatty acids in addition to statin therapy [59-62].

This research had certain limitations. There was a possibility that sampling bias existed in the studies used and there was language bias due to the database search using only English and Japanese keywords; however, all reports adopted in this study were peer-reviewed RCTs, the quality of each research was thought to be high, the bias risk was roughly not a problem, and the quality of scientific evidence could be sufficiently judged. In this systematic review, meta-analysis could not be performed due to several reasons, mainly clinical heterogeneity; however, the evidence level of an individual RCT is considered to be sufficiently high, that is, it can be said that DHA and/or EPA intake can reduce and maintain a suitable level of fasting serum TG.

In modern society, the importance of functional foods is increasing in terms of medical economics; however, it will be necessary to accumulate evidence from interventional studies targeting healthy people and perform meta-analysis.

Authors' Conclusions

The studies involving dietary interventions assessed in our review and results from healthy participants revealed that consuming 133-10,440 mg of DHA and/or EPA produces fasting serum TG lowering effects in healthy or slightly higher fasting serum TG level individuals.

Conflict of Interest

This work was funded by Maruha Nichiro Corporation. YC, HM and YT are employees of Maruha Nichiro Corporation. None of the other authors declare no conflict of interest.

Abbreviations

AA: Arachidonic acid

ALA: α-linoleic acid

CVD: Cardiovascular disease

DHA: Docosahexaenoic acid

DPA: Docosapentaenoic acid

EPA: Eicosapentaenoic acid

HDL: High density lipoprotein

LA: Linoleic acid

LDL: Low density lipoprotein

LTs: Leukotrienes

PUFAs: Polyunsaturated fatty acids

RCTs: Randomized controlled trials

TG: Triglycerides

VLDL: Very low-density lipoprotein

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