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Omega-3 polyunsaturated fatty acids (fish oil) and cardioprotective benefits

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Abstract The omega-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are found in seafood (especially fatty fish) and supplements. The lipid content and fatty acid profile vary greatly among different fish species. Fish oil supplements are generally safe and the risk of toxicity with methylmercury and environmental toxin is minimal. A wide range of studies show an inverse relationship between marine n-3 fatty acids (EPA + DHA) consumption and the risk of developing cardiovascular disease (CVD) including myocardial infarction and stroke. Omega-3 fatty acids are cardioprotective mainly due to the modulation of a number of known risk factors for CVD: improving endothelial function, lowering blood pressure and lowering triglycerides. In this mini review, we examine the various studies that have evaluated the fish oil role in CVD.

Keywords: Fish oil; n-3 fatty acids; eicosapentaenoic acid (EPA); docosahexaenoic acid (DHA); cardiovascular diseases

1. Introduction

According to the world health organization (WHO), cardiovascular diseases (CVD) are the main leading cause of death around the world. Back in 2016, 17.9 million people died with CVD, representing a rate of 31% of the total deaths in this year. Eighty five percent of deaths are due to strokes and heart attacks [1].

In the 1970s, observational studies pointed that Inuit in Greenland had a low incidence of CVD than the Danish population. The researchers Bang and Dyerberg conducted studies comparing plasma-lipid pattern and eating habits between the two populations. They concluded that there was a relationship between dietary habits and the occurrence of CVD. Inuit in Greenland were distinguished by their traditional lifestyle and in particular their special dietary habits characterized by the consumption of fish meat especially Greenland halibut, capelin, and some sort of salmon. This diet showed a higher portion of long chain polyunsaturated fatty acids especially eicosapentaenoic acid (EPA, 20:5n-3) and

docosahexaenoic acid (DHA, 22:6n-3) which are known to be the most common fatty acids revealed in marine fats [2, 3].

The American Heart Association (AHA) mentioned the importance of consuming fish. It recommends eating fish at least twice a week particularly fatty fish like salmon, mackerel, herring, lake trout, sardines and albacore tuna which contain a high percent of omega-3 fatty acids. To get the full benefits of fish, the AHA exhorts eating two 3. 5-ounce servings of non-fried fish or around 3/4 cup of flaked fish, per week. Eating at the minimum one serving per week may be better for cardiovascular health than eating no fish, particularly if it is a replacement for foods containing high saturated fat, salt and added sugar [4, 5]. The beneficial effect of fish on CVD is attributed to the content of omega-3 fatty acids [6].

The beneficial use of n-3 PUFA has been widely studied in a diverse variety of disease conditions including CVD. Numerous studies on the relationship between seafood consumption or polyunsaturated fatty acids supplements (EPA + DHA) and CVD have been realized and the positive effects of high consumption have been mentioned in these studies [7]. In this review, we discuss the amount of EPA and DHA in fish species and summarize the results of studies evaluating the relationship between the intake of marine omega-3 supplements or fish consumption and the risk of CVD.

2. **Search methods**

We performed an online search on PubMed and ScienceDirect databases using a combination of keywords to facilitate the search process (cardiovascular disease, omega-3, fish oil, polyunsaturated fatty acids, EPA, DHA, fish).

The selected articles were divided into two sections. The first one is related to the EPA and DHA concentration in fish species and the second one to studies evaluating the relationship between omega-3 fatty acids and CVD.

The articles were selected on the basis of the following criteria:

Eligibility criteria

- Articles written in English.
- Articles based on Human studies.
- Randomized controlled trials RCT and Cohort studies.
- Articles published from 2000 to 2020.

3. Results

3.1-Overview of fat content, DHA and EPA profile and ω-3/ω-6 ratio in fish species.

Nine different edible fish species from marine water were selected, among the species studied Pacific herring that contain the highest amount of fat (10.78%) followed by Indian oil sardine (9.2%) (Table 1). According to the lipid content Pacific hake, croaker and spotted rose snapper are classified in the category of lean fish (less than 2%), whereas green jack and pink salmon are classified as low-fat fish (2–4%).Yellowtail amberjack and mackerel are classified as medium-fat fish (4–8%). For Indian oil sardine and pacific herring, represent the high-fat fish (over 9%) [8].

It is essential to mention that the fatty acid values selected and listed in the table are unstable because it is well known that the content of lipids in fish can vary considerably through-out the year depending on the catch season, which in turn is affected by the life cycle of fish or water temperature [9].

Significant variation in the proportion of total PUFA was detected in the fish species. It ranged between 24.21% in high fat Pacific herring and 48.30% in the low fat Pacific hakes (Table 1). There is a negative correlation between the fat content and PUFA concentration especially in Pacific fish species [8]. The proportion of DHA varied signantifically between these fish species .It was higher in the lean, low fat and medium-fat fish (from 16.28% to 24.55%) than in the high-fat fish species (6.90% in Indian oil sardine and 8.58% in Pacific herring). The highest DHA content was revealed in Pacific Hake (24.55%) (Table1).

The EPA content varied in a lower degree than the DHA content among the fish species, ranging from 4.32% to 15.85% in the lean, low-fat and medium-fat fish and for the high-fat fish species: 8.74% in Pacific herring and 12.30% in Indian oil sardine. Once again, Pacific Hake showed the highest proportion of EPA (15.85%) (Table 1).

Table 1. Lipid content (g/100 g wet weight), proportion of PUFA, EPA and DHA and Ω3/Ω6 ratios) in nine fish species.

PUFA: polyunsaturated fatty acids.

Scientific name	Common name	Lipid content % g/100g wet weight	∑ PUFA %	EPA %	DHA %	EPA+DHA mg/100 g wet weight	Ω3/Ω6	Ref
Seriola lalandi	Yellowtail Amberjack	4.59	32.60	4.32	21.32	915.76	12.25	[9]
Merluccius gayi gayi	Pacific Hake	1.29	48.30	15.85	24.55	340.21	11.50	[9]
Cilus gilberti	Croaker	1.44	41.29	11.72	20.61	344.69	10.96	[9]
Scomber japonicus	Mackerel	6.44	32.48	7.06	16.28	1676.95	7.31	[9]
Caranx caballus	Green jack	3.74	33.66	7.09	19.65	898.00	8.12	[11]
Lutjanus guttatus	Spotted rose snapper	1.81	27.90	4.84	16.11	342.00	5.90	[11]
Sardinella longiceps	Indian oil sardine	9.2	26.80	12.30	6.90	1472.90	4.30	[12]
Clupea harengus pallasi	Pacific herring	10.78	24.21	8.74	8.58	1680.00	7.35	[8]
Oncorhynchus gorbusha	Pink salmon	3.95	38.89	8.17	19.34	970.00	9.55	[8]

EPA: eicosapentaenoic acid.
DHA: docosahexaenoic acid.

All species reviewed contained higher proportions of *ω*-3 than *ω*-6 PUFA. The oils of the fish species selected contained a high Ω3/Ω6 ratio (ranging from 4.30 to 12.25) (Table 1). Yellowtail Amberjack had the highest value, followed by Pacific hake, croaker, pink salmon, green jack, pacific herring, mackerel, spotted rose snapper, and Indian oil sardine.

In terms of the absolute amount of DHA + EPA, the highest DHA + EPA, content was detected in both Pacific herring (1680.00 mg/100 g wet weight) and Mackerel (1676.95 mg/100g wet weight). Herring, which had the highest fat content out of all the selected fish species.

The main contributor to n-3 PUFAs was DHA followed by EPA. DHA and EPA together represented more than 70% of the total PUFA in these fish species.

According to the US Department of Agriculture (USDA), daily intake of EPA + DHA should be at least 250 mg [10]. To satisfy the daily recommendation, it would be needed to consume approximately 28g of Yellowtail Amberjack, 74g of Pacific Hake, 73g of croaker, 15 g of mackerel ,28 g of green jack, 74g of spotted rose snapper, 17g of Indian oil sardine, 15g of Pacific herring and 26g of pink salmon.

3. 2-Cardioprotective benefits of ω-3 PUFAs.

The biological effects of fish on blood pressure are hypothesized to result from the vasodilating effects of prostaglandin metabolites of n-3 LC PUFAs. To date, a wide range of trials have shown the hypotensive effects of fish oil supplements in both hypertensive and non-hypertensive individuals. Major studies, several systematic reviews and meta-analyses have demonstrated inverse relationships between fish consumption and dietary n-3 PUFAs supplements and the risk of CHD in healthy populations.

Table 2. A summary of the main outcomes of eight studies.

Reference	Study design	Year	Main conclusion
[13]	A Randomized, Controlled Clinical Trial	**2015**	The administration of fish oil decreased both aortic pulse pressure and aortic augmentation pressure. This was only observed when 6 g of fish oil was administrated in isolation, without adding multivitamin.
[14]	A Secondary Analysis of a Randomized Clinical Trial	**2018**	High doses of EPA and DHA can be beneficial for patients with coronary artery disease (CAD) by maintaining physical function, increasing the amount of exercise and reducing joint replacement. EPA and DHA may be a safe preventive intervention against musculoskeletal symptoms in patients with CAD.
[15]	A Randomized Clinical Trial	**2016**	DHA significantly decreased postprandial triglyceride (TG) concentrations. The specific cardiovascular protective effects of EPA can be partially attributed to its ability to reduce Lp-PLA2, an important risk factor for CVD.
[16]	A Randomized Clinical Trial	**2016**	The study showed a beneficial effect of highly dosed omega-3 fatty acids treatment on adverse left ventricular remodeling after acute myocardial infarction (MI) in patients receiving modern guideline therapies.
[17]	Cohort study	**2002**	Among women, a significant inverse correlation between omega-3 fatty acids and fish consumption and the incidence of major coronary heart disease (CHD). Particularly CHD deaths.
[18]	Cohort study	**2003**	Among adults aged ≥65 years, modest intake of tuna or other grilled or baked fish, but not fried fish or fish sandwiches, is

			related to a lower risk of ischemic heart disease (IHD). In particular arrhythmic IHD deaths.
[19]	Randomized controlled trial	**2017**	Combined EPA and high-dose pitavastatin (PTV) therapy led to a greater reduction in coronary plaque than pitavastatin (PTV) therapy alone. Particularly, the volume of lipid plaques was reduced by the added EPA therapy, specifically in patients with stable angina pectoris.
[20]	Randomized Clinical Trial	**2017**	Higher doses of eicosapentaenoic acid and docosahexaenoic acid provided additional benefit to statins in the prevention of fibrous coronary plaque progression in patients receiving treatment with well-controlled low-density lipoprotein cholesterol levels.

The n-3 PUFAs provide pleiotropic anti-inflammatory effects. They can easily replace arachidonic acid in cell membranes, n-3 PUFAs produce lower potency inflammatory substrates, EPA and DHA are metabolized to anti-inflammatory mediators [12].

Omega-3 fatty acids may not only prevent the development of plaque but also contribute to its stabilization, supplementation with omega-3 fatty acids can significantly increase tissue concentrations of EPA and DHA and decrease macrophage infiltration and fibrous plug thickening in the human cardiovascular arteries [13, 14].

Decreased physical activity is a known risk factor for CVD. The n-3 PUFAs have been reported to improve exercise tolerance. This can be attributed to favorable effects on erythrocyte rheology and skeletal muscle function [15].

The main outcomes of eight studies were summarized in Table 2. Six RCTs and two cohort studies showed the beneficial side of n-3 PUFAs on different CVD. (Table 2)

4. Discussion

Omega−3 fatty acids are polyunsaturated fatty acids (PUFAs) with a carboxylic acid group at one end and methyl group at the other end (Figure 1). They are characterized by the presence of the nearest double bond to the methyl end on carbon number three, if the methyl carbon is counted as number one (Figure 1). EPA and DHA are the most important n-3 fatty acids [16].

Fish and seafood are considered as a rich source of highly unsaturated fatty acids, especially DHA and EPA (10). Out of the selected fish species, Pacific herring, Indian oil sardine and Mackerel are very rich in EPA and DHA. Based on the minimum intake of EPA+DHA recommended by USDA (250mg/day), these fishes can be served as natural dietary supplements for both EPA and DHA to satisfy this daily recommendation.

The intake of EPA and DHA from diet is strongly influenced by fish consumption because fish, especially fatty fish are the most rich dietary source of these fatty acids [17].

Published estimations of the intake of long chain n-3 PUFAs vary considerably between studies and countries. The highest intakes of EPA + DHA are found in Japan, Norway and Spain, which is likely due to the higher consumption of fish in these countries. Lower intakes of EPA + DHA were found in the United States due to lower consumption of fish and fatty fish [17, 18].

Omega-3 fatty acids become an important part of diet in the prevention of cardiovascular disease [19]. Numerous studies have been conducted to investigate the beneficial effects of consuming these fatty acids in the form of fish oils, capsules or seafood [20]. Most of these studies concluded that increased seafood consumption is beneficial and can help prevent the development of cardiovascular disease, in particular by reducing fatal events related to cardiovascular disease [21, 22].

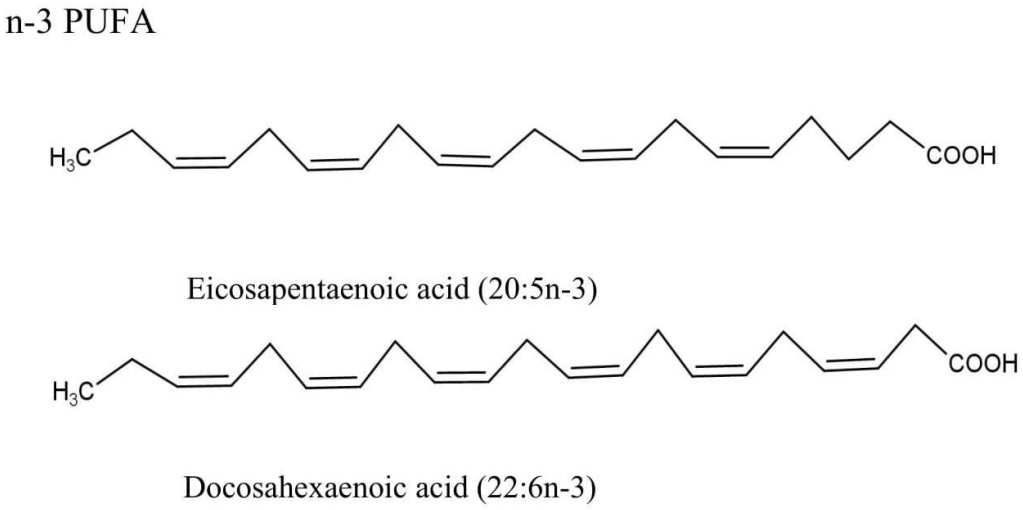

Figure 1. *Structure of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). (The structures were designed by the application KingDraw Chemical Structure Editor)*

In 2010, the European Food Safety Authority (EFSA) concluded that, in the general population, EPA and DHA contribute to the preservation of normal heart function, normal blood pressure and normal blood triglyceride levels [7].

There is a wide body of evidence based on long-term prospective cohort studies that have reliably exposed a significant association between higher intakes of fish, fatty fish and marine n-3 fatty acids (EPA+DHA) and a lower risk of development of CVD, specifically CHD, having an MI, heart attack and death from CVD in the general population [17].

The antiarrhythmic properties, that might protect against death from CHD, were highlighted in marine-derived long chain omega-3 polyunsaturated fatty acids (PUFAs), mainly eicosapentaenoic acid and docosahexaenoic acid, have [23].

Credible cardioprotective effect of EPA and DHA is based on the strong mechanisms of EPA and DHA by modulating a number of known risk factors for CVD, such as heart rate, heart rate variability, blood lipids, blood pressure, platelet aggregation, inflammation and endothelial [17]. Furthermore, these omega-3 fatty acids reduce the risk of CVD by decreasing blood triglyceride (TG) levels, increasing

high-density lipoprotein (HDL) levels, lowering blood pressure, improving heart rate variability, reducing heart rate, affording potent anti-inflammatory and antithrombotic effects [24].

On the other hand, recent large-scale studies, in both primary and secondary prevention, have failed to prove any benefit of fish oil supplements on CVD [11].

A randomized, placebo-controlled trial study included a total of 25,871 participants has assessed the effect of vitamin D3 (2000 IU per day) and marine n−3 fatty acids (1 g per day) supplementation in the primary prevention of CVD and cancer. During a 5-year follow-up, supplementation with n-3 fatty acids did not lead to a lower incidence of major cardiovascular events or cancers in comparison to placebo [25].

A double blind, randomized, placebo controlled trial (n= 2501 French patients with a history of coronary or cerebral ischemic event) have assessed the effects of B-vitamin and n−3 PUFA supplementation. The supplementation did not significantly affect the major cardiovascular events. These results could be illuminated by the insufficient of period supplementation, the follow-up and doses used for B vitamins and omega-3 polyunsaturated fatty acids [26].

5. Conclusion

Several epidemiologic and observational studies have revealed and supported the cardioprotective benefits from fish and fish oil consumption. Regular consumption of non-fried fish and seafood is recommended to promote health. Supplement fish oil containing EPA and DHA has a safe profile and may be a reasonable alternative, in particular for individuals with pre-existing CVD. In addition, the increased intake of omega-3 PUFAs has been related to a wide range of other health benefits, including a decreasing risk of prostate cancer, depression, inflammatory bowel disease. Further studied are need to highlight benefits and mechanisms of effects.

Disclosure Statement

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. No additional external funding was received for this study.

Author Contribution

OA, drafted the paper, NK designed and revised the paper. All authors have approved the paper.

Conflict of Interest

The author declares that no competing interests exist.

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