Omega-3 supplements, including EPA and DHA for Cardioprotection: A Review

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Abstract

People can make fats using building blocks known as fatty acids, and these fatty acids are known as non-essential, as we are not dependent on obtaining them from the food we eat. However, there are certain fatty acids that we cannot synthesize by ourselves, but are essential to our health. These essential fatty acids include omega-3 fatty acids, which contain the fish oil derived eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). EPA and DHA have important biological functions including effects on membranes and gene transcription. Studies have indicated that the use of fish oil is associated with coronary heart disease risk reduction. There are a number of proposed mechanisms responsible for the beneficial effects of omega-3 fatty acids such as decreasing arrhythmias, lowering heart rate and blood pressure, decreasing platelet aggregation and lowering triglyceride levels. On the other hand, findings provide evidence that associations observed in studies suggesting a benefit of fish or omega-3 fatty acid supplementation is due to a convergence of greater fish intakes and an overall healthier dietary pattern, rather than to the omega-3 fatty acid alone. The focus of this paper is to review the potential mechanisms by which these fatty acids, in supplement form, reduce cardiovascular disease risk.

Introduction

Greenland Eskimos are responsible for some of the interest that surrounds omega-3 fatty acids and fish oils. In the 1960's, Danish and British scientists wondered how Eskimos could eat the highest fat diet in the world without suffering from heart attacks. Researchers traveled to remote areas in Greenland to study Eskimos whose traditional diet included fatty fish and blubber packed seals. Regardless of their enormous fat intake, the Eskimos' bloods was found to be typically neither sticky nor thick, took a very long time to clot, in addition to their cholesterol and fat levels in their blood were considerably very normal ("Why Take Fish Oil Supplements", 2009).

These specific discoveries related to the Eskimos diet explained the low rate of heart attacks, and the lack of blood clots in the arteries among this group of people. The fat in the fish and the sea mammals that comprised a major portion of the Eskimos' diet, which has been related to their positive cardiovascular health, is full of long-chain omega-3 fatty acids, including EPA and DHA, which, in turn, provide the sea mammals and fish with fluid cell membranes, flexible tissues and temperature control for Greenland's icy waters ("Why Take Fish Oil Supplements", 2009).

The term 'fish oil' is most commonly associated as a collective name for docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), and both EPA and DHA are components of omega-3 fatty acids. Fish oil and omega-3 fatty acids are known as essential fatty acids because one's body cannot produce these fatty acids, and therefore an individual must rely on diet and supplementation to obtain these essential fatty acids.

Omega-3 fatty acids can be incorporated into the diet through the consumption of fish, such as salmon, tuna, and halibut, some plants and also nut oils.

Omega-3 fatty acids play a crucial role in brain function, as well as in normal growth and development. However, these essential fatty acids have become increasingly more popular in the supplementation world because of the proposed benefits, including brain and cardiovascular protection, but also for overall general well-being. Some would say that omega-3, fish oil supplements are considered to be the biggest selling supplement in health food stores, pharmacies, and online retail stores.

Since the first American Heart Association Science Advisory "Fish Consumption, Fish Oil, Lipids, and Coronary Heart Disease," there have been new findings and evidence from randomized controlled trials that have reported the beneficial effects of omega-3 fatty acids on cardiovascular disease in patients with preexisting CVD as well as in healthy individuals. Furthermore, the American Heart Association (AHA) has supported the use of omega-3 fatty acids for secondary prevention of cardiovascular events in people with coronary heart disease. The current recommendation is 1g/day of a combination of EPA and DHA. Although the current recommendation identifies oily fish as the ideal source, such as salmon, tuna and sardines, fish oil (in capsule or liquid form) is also an acceptable option. The omega-3 fatty acid recommendation is based on an extensive and growing body of evidence supporting the cardiovascular benefits and triglyceride-lowering effects of omega-3 fatty acids. Furthermore, the Food and Drug Administration (FDA) has approved an omega-3 fatty acid formulation, at a dosage of 4.0g/day, for the treatment of very high triglyceride levels (Lee et al., 2008).

Omega-3 fatty acids have been shown in epidemiological and clinical trials to reduce the incidence of cardiovascular disease. Proposed mechanisms for these effects include reduced triglyceride concentrations, antiarrhythmic effects, decreased platelet aggregation, plaque stabilization, reduced blood pressure and an overall reduced heart rate. In addition, effects include reduction in levels of thromboxane, the prostaglandin that promotes artery constriction and blood clotting, thinner blood leading to improved circulation and increased flexibility of red blood cell membranes, which make it easier for blood to flow through small capillaries (Lee et al., 2006).

Collectively, data has supported the recommendation made by the American Heart Association Dietary Guidelines to include at least two servings of fish per week, specifically fatty fish. In addition, data supports including vegetable oils such as canola and flaxseed oils and food sources (walnuts or flaxseeds) high in omega-3 fatty acids in a healthy diet for the general population. In addition, evidence from prospective secondary prevention studies proposes that omega-3 fatty acid supplementation, including EPA and DHA, ranging from 0.5 to 1.8g/day (either as fatty fish or supplements), significantly reduces subsequent cardiac events and mortality. However, many are still confused about the appropriate form, indications and actual dosing of omega-3 fatty acids.

This review will summarize findings from four peer reviewed research articles surrounding the proposed mechanisms of omega-3 and fish oil supplementation in relation to cardiovascular disease prevention, the proposed mechanisms for secondary prevention of cardiovascular disease , and all or what portion of the population could benefit from supplementation for cardiovascular health (Harris et al, 2007). Moreover, this review will examine any differences between proposed benefits when consuming fish and omega-3 supplements for cardiovascular health.

Discussion

Cardiovascular Disease

In the article, 'Omega-3 Acids for Cardioprotection', Harris et al. examines the evidence for the cardiovascular benefits provided by omega-3 fatty acids in the form of supplementation. The most convincing evidence comes from three large controlled trials of 32,000 participants who were randomized to receive omega-3 fatty acid supplements containing both DHA and EPA or to act as the controls. The trials presented reductions in cardiovascular events of 19-45%. These findings support that the intake of omega-3 fatty acids, whether from dietary sources or fish oil supplements, should be increased, especially for those with or at risk for coronary heart disease. Additionally, it is suggested that patients with hypertriglyceridemia consume DHA and EPA in a dose of 3-4 g/day in order to lower triglyceride levels.

Harris et al. concluded that clinicians target between 3-4 g/day in order to see a meaningful triglyceride lowering effect. Also, since there have been no trials comparing DHA and EPA with cardiovascular disease as an end point, neither of these omega-3 fatty acids can be conclusively said to be more cardioprotective than the other. Furthermore, this review did not include any randomized controlled trials that examine omega-3 fatty acids as a preventative measure for cardiovascular events and mortality in a primary prevention population.

Additionally, although well designed trials presented by the others showed significant benefits for omega-3 fatty acids in patients with established coronary artery disease, other studies have not reported positive outcomes. Some studies have not reported a beneficial association of fish consumption or supplementation with coronary heart disease mortality. In the Health Professionals' Follow-up Study, no significant association was observed between omega-3 fatty acids and risk of any coronary heart disease risks including sudden death. Likewise, the U.S. Physicians Health Study did not show an association between fish consumption or omega-3 fatty acid supplementation and reduced risk of total myocardial infraction, sudden cardiac death, or total cardiovascular mortality (Harris et al., 2008).

The authors also suggest that despite the results from trials showing no treatment effects, omega-3 fatty acid supplements should be given in conjunction with health lifestyle changes. There is overall sufficient strong evidence to provide the public with recommendations to increase omega-3 fatty acids in both primary and secondary prevention. Some investigators have speculated that the conflicting data from the epidemiological studies reflect differences in definitions of sudden death and also the presence of confounding factors such as the reference group and the specific lifestyles of the participants (Harris et al., 2008).

A limitation for the study conducted by Harris et al. is that at the time of the review, the only randomized control trial of omega-3 fatty acids in secondary prevention of coronary heart disease was the Diet And Reinfarction Trial (DART). This trial reported a 29% reduction in mortality over a two year period in many myocardial infraction survivors. These participants were advised to increase their intake of oily fish (200 to 400 g of fatty fish per week).

However, Harris et al. later reviewed omega-3 fatty acids in relation to cardiovascular disease in the article, "Omega-3 fatty acids and coronary heart disease risk: Clinical and mechanistic perspectives", where randomized controlled trials were designed to detect the effects of supplemental EPA and DHA in clinical events. Patients were admitted to the hospital with suspected acute myocardial infractions and were randomized to either fish oil capsules (EPA and DHA), mustard oil (ALA), or placebo. After one year, total cardiac events were 25% and 28% in the fish oil and mustard oil groups, compared to 35% in the placebo group. As in the DART, nonfatal myocardial infractions were significantly reduced in the fish oil and mustard oil groups. Most currently, epidemiological studies and randomized controlled trials show a beneficial effect of dietary and supplemental omega-3 fatty acids, including both EPA and DHA on cardiovascular disease (Harris et al., 2008).

A common bias for research can arise from where funding is coming from for the project. In "Omega-3 fatty acids and coronary heart disease risk: Clinical and mechanistic perspectives", Dr. Harris received research grants from both Monsanto Company and Reliant Pharmaceuticals, both of where he is a consultant. Also, Dr. Tighe, another researcher on the team, has a link to Reliant Pharmaceuticals. One must take into consideration the recommendations from this particular paper based on the relationships of the researchers to the companies that produced the grant funding for the project.

Mechanisms

Triglycerides

The hypotriglyceridemic effects of omega-3 fatty acids from fish oils are well established from previous human studies. In the article, 'Omega-3 fatty acids and coronary heart disease: Clinical and mechanistic perspectives', Harris et al. reported that 4 g/day of omega-3 fatty acids from fish oil decrease serum triglyceride levels by 25-30%. In addition, LDL cholesterol and HDL cholesterol also increase, which demonstrates a relationship between omega-3 fatty acid intake and triglyceride lowering (Harris et al., 2007).

The two specific omega-3 fatty acids that have been associated with cardiovascular benefits and triglyceride lowering effects are from EPA and DHA. Fish oil also plays a role in the treatment of hypertriglyceridemia, with effective doses ranging from 3-5 g/day, which can only be consistently obtained through supplementation. Harris et al. reviewed 25 trials that evaluated the risks of coronary artery disease events as a function of in vivo omega-3 fatty acid levels. Omega-3 fatty acids, either in the form of oily fish or fish oil capsules, reduced mortality by 29% in post-myocardial infraction patients in addition to significantly reducing the risk of sudden cardiac death by 45%. Additionally, omega-3 fatty acids are associated with significant reductions in systolic and diastolic blood pressure. Presently, there is evidence surrounding both EPA and DHA having triglyceride-lowering properties (Harris et al., 2007).

Blood Pressure

Omega-3 fatty acids have a relatively small, dose-dependent, hypotensive effect, which depends on an individual's severity of hypertension. Appel et al. found that blood pressure was decreased in trials of untreated hypertensive patients given >3g/day of omega-3 fatty acids. Furthermore, DHA seems to be more effective than EPA in lowering blood pressure. The first mechanism that can account for this effect is related to the incorporation of EPA and DHA into membrane phospholipids increasing systemic arterial compliance. In addition, EPA and DHA can improve endothelial function, while fish oil intake can also reduce overall heart rate. The dose required to lower blood pressure is still in review, but it is clear that an increased intake of omega-3 fatty acids does have a minor role in the management of hypertension (Harris et al., 2008).

Thrombosis

The antithrombotic potential of omega-3 fatty acids was one of the first effects to be reported in Greenland Eskimos, who consume large amounts of whale and seal meat. While omega-6 fatty acids can enhance thrombosis, the omega-3 fatty acids have the opposite effects. Omega-3 fatty acids can decrease platelet aggregation, which results in the maintenance of bleeding times. Although there is evidence that omega-3 fatty acids beneficially influence collagen-induced platelet aggregation, their effects on thrombosis remain unclear. There is little evidence linking an intake of <3 g/day of omega-3 fatty acids to cause clinically significant bleeding (Harris et al., 2008).

Arrhythmias

The cardioprotective effects of fish oil have been related to antiarrhythmic effects of EPA plus DHA. The proposed mechanisms to explain the effects are not centered around lipid or blood pressure lowering, or antithrombotic effects, but on the stabilizing capability of omega-3 fatty acids on the heart. There are several mechanisms to account for the effects of the antiarrhythmic action of omega-3 fatty acids, which include the capability of omega-3 fatty acids to potentially alter both eicosanoid production and ion-channel function. Omega-3 fatty acids may produce an antiarrhythmic action by preventing cystolic free calcium levels from reaching toxic levels in cardiac myocytes.

Other Biological, Lifestyle, and Dietary Effects

In the article, 'Relation of Omega-3 Fatty Acid Intake to Other Dietary Factors Known to Reduce Coronary Heart Disease Risk', Cundiff et al. examines the data surrounding the correlation of fish oil or omega-3 fatty acid supplement consumption and coronary heart disease benefits. Using the Diabetic Control and Complications Trial (DCCT) database, correlations between consumption of omega-3 fatty acids and saturated fatty acids to dietary variables and to age, gender, exercise level and tobacco use were tested using Pearson correlation coefficients. According to the DCCT database

consisting of 1,441 subjects, omega-3 fatty acids were inversely correlated with an overall low risk nutritional profile for coronary heart disease. Overall, the findings suggest that associations observed in studies indicating a benefit from omega-3 fatty acids may be due to a combination of higher fish intakes with overall healthier dietary patterns rather than with a specific effect of supplementation alone (Cundiff, Lanou & Nigg, 2007).

The evidence surrounding the benefits of omega-3 and fish oil supplementation continues to grow. Harris et al. presents the notion that more clarity regarding possible advantages of supplementation is needed to further address the question of whether high levels of omega-3 fatty acids and or fish consumption might decrease the risk of cardiovascular disease. Another proposed idea is that the lack of fish consumption is related with eating more saturated fatty acids and high saturated fatty acid intake relates to more smoking and less exercise. Furthermore, lifestyle factors and dietary factors may confound the relation of fish consumption to cardiovascular disease (Cundiff, Lanou & Nigg, 2007).

Intake of Omega-3 Fatty Acids

The intake of omega-3 fatty acids in the United States is about 1.6 g/day. Fish is the major source of EPA and DHA and the quantities vary among species. Patients with cardiovascular disease should be encouraged to increase their consumption of EPA and DHA to 1g/day. The level of EPA and DHA may be difficult to achieve solely through fish consumption, so an omega-3 supplement or fish oil supplement should be considered. The most common fish oil capsules sold in the United States provides 180mg of EPA and 120mg of DHA per capsule (Harris et al., 2008).

The aim of the review, 'Dietetic guidelines on food and nutrition in secondary prevention of cardiovascular disease- evidence from systemic reviews of randomized controlled trials', by Mead et al., was to examine the evidence on dietary advice to prevent further events in people with existing cardiovascular disease. It was concluded that individuals who have endured a myocardial infraction may benefit from adopting a Mediterranean type diet and increasing intakes of omega-3 fats, but it is not clear whether they are beneficial for all patients with cardiovascular disease (Mead et al., 2006).

Reviews examined in this article present results making past evidence less clear, specifically that there is no strong evidence to show omega-3 fatty acids alter total mortality of cardiovascular events in those with, or at risk of cardiovascular disease. Overall, Mead et al. suggests that it is unclear whether omega-3 advice is beneficial in all individuals with cardiovascular disease, but that it is probably protective in people who have recently had a myocardial infraction.

It is important to consider the idea that all people suffering or at risk for cardiovascular disease may not have the same beneficial effects to supplementation (Mead et al., 2006). A limitation of this review is that is does not examine the most effective way the information surrounding cardiovascular disease should be dispersed. The number of people living with cardiovascular disease is increasing and resources may be limited for most. Therefore, it is essential that further research related to cardiovascular disease should include cost-effective approaches to support ways in which

clinicians and public health advocates can spread information concerning food, diet and lifestyle to those with the disease or for those at risk for cardiovascular disease.

Conclusion

There are multiple factors that affect cardiovascular disease risk and the risk may be affected by omega-3 fatty acids. Omega-3 fatty acids have been shown in epidemiological and clinical trials to reduce the incidence of cardiovascular disease by reducing triglycerides, lowering blood pressure, thrombotic effects, and cardiac arrhythmia suppression. Furthermore, omega-3 fatty acids can decrease platelet aggregation and have the potential to enhance atherosclerotic plaque stabilization (Harris et al., 2008).

Evidence suggests that EPA and DHA supplementation ranging from 0.5-1.8g/day (either as fatty fish or supplements) significantly reduces cardiac events and mortality. The data supports the recommendation made by the American Heart Association Dietary Guidelines to include at least two servings of fatty fish per week. In addition, data supports the inclusion of vegetable oils (soybean, canola, flaxseed etc.) and food sources high in omega-3 fatty acids in a healthy diet for the general population (Mead et al., 2006).

There is strong evidence that fish oils have a strong beneficial effect on triglycerides and there is also evidence of a minor beneficial effect of fish oils on blood pressure. However, there is little data available on the specific effect of omega-3 fatty acids on cardiovascular disease risk factors and how the effects may be different depending on one's underlying conditions and risk for the disease. Also, there is little data surrounding beneficial effects of omega-3 fatty acid regarding the amount that should be consumed, duration of the consumption, or the specific source of omega-3 fatty acids. Specifically, few studies have analyzed all the current data on cardiovascular disease risk or compared doses or the types of omega-3 fatty acids that were consumed by the individuals. Furthermore, many reviews and studies have not accounted for confounding factors in the populations or have used any eligibility criteria for the participants.

Since there are some limitations from the current evidence on omega-3 fatty acids and cardiovascular disease, there are recommendations that can be addressed for future research. Future studies on the disease risk factors should address the effects of omega-3 fatty acids in different populations, including those of differing disease states. Also, studies should address different covariates such as dose and duration of intake that may affect beneficial outcomes of supplementation. In addition, further investigation is needed to determine the effects of higher fish intake compared to supplementation for individuals at risk or who currently have cardiovascular disease.

Works Cited

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