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Dietary Effects of Fish Oils on Human Health: A Review of Recent Studies

SACHI. SRI KANTHA, Ph.D.

Department of Food Science, University of Illinois, Urbana, Illinois

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The beneficial effects in humans of ingesting fish oils have attracted much attention among medical scientists and nutritionists recently. Human studies conducted in populations of Eskimos, Japanese, and Caucasians since 1970 are reviewed in this paper. The evidence shows that a diet rich in omega-3 fatty acids significantly reduces plasma cholesterol and triglyceride levels, improves fat tolerance, prolongs bleeding times, reduces platelet counts, and decreases platelet adhesiveness.

INTRODUCTION

Three research studies on the beneficial effects of fish oil on human health, which were published in a single issue of the *New England Journal of Medicine* in 1985 [1,2,3] attracted much attention to the nutritional properties of fish oils. Glomset [4] observed in an editorial in this particular issue that these studies *(a)* emphasize the fact that different types of polyunsaturated fatty acids can have vastly different metabolic effects and *(b)* raise questions in particular about the relation of omega-3 polyunsaturated fatty acids to human development, growth, and disease. In addition, a triglyceride-lowering effect of marine polyunsaturates in patients with hypertriglyceridemia [5] and studies on feeding fish oil concentrate to stroke patients [6] were also reported. In view of these findings, a review of recent literature on the human studies of the beneficial effects of ingesting fish oils seems pertinent.

An excellent, extensive review by Stansby [7] covers wide areas such as chemistry, sources, and nutritional properties of fish oils. Ackman [8,9] surveyed in depth the literature published since 1950 on fish lipids and fatty acid composition of fish oils. Studies on auto-oxidation and measurement of oxidation have been reviewed by Hardy [10]. Biological information on the long-chain mono-enoic fatty acids in partially hydrogenated oils has been compiled in the symposium proceedings edited by Barlow and Stansby [11].

In this review, studies reported since 1970 on the effects of fish oils on human health are considered. For literature published in the pre-1970 period, the reader should refer to the earlier reviews [7,12,13,14,15].

FATTY ACID COMPOSITION

Herring, menhaden, pilchard, sardine, and whale are the major sources of fish oils. Although whales are marine mammals, because of their ecological, functional, and physiological similarities to fish, whale oil is included in the category of fish oils. In this

Address reprint requests to: Sachi. Sri Kantha, Laboratory of Marine Biochemistry, Faculty of Agriculture, University of Tokyo, Bunkyo-ku, Tokyo 113, Japan

review, only the dietary effects of fish oils are considered, and oils from aquatic invertebrates such as shrimp, crabs, oysters, and small crustaceans are not included.

According to the compilations of Weiss [16], iodine values reported for herring, menhaden, pilchard, and sardine range from 148 to 200. The whale oil has an iodine value range from 110 to 135. (Iodine value is a measure of unsaturation of oil and is defined as the percentage of iodine that will be absorbed by a chemically unsaturated substance in a given time.) The predominant polyunsaturated fatty acids in the oils of herring and menhaden are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Pilchard, sardine, and whale oils are rich in arachidonic acid (AA). The classic monograph on the chemical composition of natural fats by Hilditch and Williams [17] provides an exhaustive listing of the fatty acid components of marine elasmobranch fish (liver fats), marine teleost fish (liver fats and body fats), freshwater fish, salmon, eel, sturgeon, tuna, grouper, and the whale family.

One of the most prominent specific component acids of fish oils in hexadecenoic acid $C_{16}H_{30}O_2$. Polyenoic acids of the C18, C20, C22, C24, and even, perhaps, C26 series contribute to the ready auto-oxidation of fish oils. Of these, the C20 and C22 groups of polyunsaturated fatty acids are most abundant in fish. The degree of unsaturation among fatty acids is an indication of the number of double bonds in the molecule. The larger the number of double bonds, the higher the degree of unsaturation present in the polyenoic acid. The location of the double bond in the molecule is denoted by counting from the methyl (omega) terminus. Omega-6 and omega-3 families of dietary unsaturated fatty acids are of clinical interest. In the omega-3 family, the first double bond is located on the third carbon atom from the methyl end; the omega-6 family has the first double bond located on the sixth carbon atom from the methyl end. Arachidonic acid (C20:4) belongs to the omega-6 family; eicosapentaenoic acid (C20:5) and docosahexaenoic acid (C22:6) belong to the omega-3 family.

Cod liver oil is the most widely used of the fish liver oils, as a consequence of its medicinal value. Hilditch and Williams [17] reported that on a percentage weight basis, the cod liver oil is rich in EPA (9.3 percent), DHA (8.7 percent), and AA (2.2 percent). Though in the U.S.A. fish oils are not used for edible purposes, they are used extensively in Canada and Europe for the manufacture of shortenings and margarine [16]. Other ethnic populations such as Eskimos and Japanese consume large quantities of oils of marine origin, due to their accessibility and the social evolution of seafood eating habits.

STUDIES ON THE ESKIMO POPULATION

A series of prospective studies on Greenland Eskimos conducted by Dyerberg's group [18,19,20,21,22,23,24,25,26,27,28] revealed that the rarity of ischemic heart disease and the decreased thrombous tendency in this population could be linked to the ingestion of omega-3 fatty acids, derived largely from whale, seal, and fish. Dyerberg [29] and Dyerberg and Jorgensen [30] reviewed their studies on the influence of marine oils on lipoprotein metabolism in Greenland Eskimos. A coherent picture has emerged, pointing to fish oils as a major factor responsible for the low incidence of thrombotic disorders in Eskimos. Some salient facts are:

1. Eskimos eat more mono- and polyunsaturated fat at the expense of saturated fat. In addition, the polyunsaturated fats belong mainly to the marine omega-3 class. On a caloric intake of 3,000 kcal/day, 4.6 percent of C20:5 omega-3 fatty acid corresponds to an intake of 5.7 g EPA per day [20,26].

2. Eskimos have lower plasma triglyceride and cholesterol levels (in comparison to the Danish population) due to lower LDL and VLDL concentrations. Expatriate Eskimos living in Denmark did not differ in their plasma lipid and lipoprotein levels from Caucasian Danes. Thus, it could be inferred that the findings were not necessarily of genetic origin but were due to the influence of exogenous factors, presumably dietary [18,21].
3. The ratio of EPA to AA (by percentage weight in blood plasma), the precursors for prostaglandin synthesis, ranged for Eskimos from 1.5 to 2.7 in the three lipid groups, triglycerides, phospholipids, and cholesterol esters, compared to 0.2–0.5 for Danes [19,25].
4. Eskimos had bleeding times significantly longer than those of Danes, but the bleeding times of expatriate Greenlanders living in Denmark did not differ from those of other Danes. It was also demonstrated that the prolongation of bleeding time was due to a decreased platelet aggregability, accompanied by a shift in platelet fatty acid composition from the omega-6 to the omega-3 family [24].
5. Immunoreactive anti-thrombin-III (AT-III) or heparin co-factor in blood serum was found to be significantly higher in Greenland Eskimos than in expatriate Eskimos, who themselves had significantly higher levels than Danish controls.

However, Dyerberg [29] also cautioned about the pitfalls of obtaining medical statistical data from a society such as that in Greenland, which changes quickly as the original pattern of life style vanishes. This constantly changing social fabric and life style of the Eskimos could in turn eliminate the very factors which are actively investigated by the researchers.

STUDIES ON THE CAUCASIAN POPULATION

Following the trend-setting contributions by Dyerberg's group, human volunteer feeding experiments have been conducted by researchers from other countries as well [31,32,33,34,35,36,37,38,39,40,41,42]. Efforts were made to show that a supplementation of omega-3 fish polyunsaturated fatty acids to the Western-style diet could result in a depression of platelet aggregability accompanied by an increase in omega-3 polyunsaturated fatty acids in the platelet lipids.

To find out whether salmon oil feeding would result in the uptake of omega-3 fatty acids into platelets and whether platelet function would be inhibited or bleeding times prolonged, Goodnight et al. [35] conducted a prospective, controlled trial. Six male and five female volunteers were fed diets containing salmon oil and salmon. It was observed that diets containing salmon oil led to the incorporation of EPA in the phospholipid fraction of fatty acids in platelets (6.1 percent by weight) with a reduction in AA. The ratio of EPA to AA increased from 0.0045 on the control diet to 0.3 on the salmon diet. Bleeding times were prolonged from 6.75 to 10 minutes, and platelet retention on glass beads was mildly reduced from 89 percent to 78 percent. Goodnight et al. [35] concluded that in normal subjects dietary omega-3 fatty acids derived from salmon oils were incorporated into platelet phospholipids and that these changes were accompanied by alterations in bleeding time and platelet function.

Thorngren and Gustafson [34] also studied the effect of a diet rich in EPA on platelet phospholipid fatty acid composition, platelet aggregation, and bleeding time in ten healthy Swedish students. The diet of the volunteers was partly replaced by fish for eleven weeks, and this diet provided 2–3 g of EPA per day. The fish diet prolonged bleeding time by 42 percent and decreased platelet aggregability. The changes in platelet phospholipid fatty acid composition consisted of increases in the omega-3 series (C20:5 and C22:6) and decreases in the omega-6 series (C18:2 and C20:3). The authors inferred that a diet rich in omega-3 polyunsaturated fatty acids reduces the interaction between platelets and the vessel wall by mechanisms which are more complex than just a reduction in susceptibility of platelets to the naturally occurring agents collagen and ADP, or an imbalance between pro-aggregatory and anti-aggregatory prostaglandin derivatives.

Harris et al. [36] reported a metabolic study designed to determine the effects of a diet rich in omega-3 fatty acids from salmon oil upon the plasma lipids and lipoprotein in twelve normal subjects (mean age 40 ± 13.3 years) under controlled conditions. This diet was compared to two control diets, one containing levels of saturated fat typical of the American diet and the other rich in omega-6 polyunsaturated linoleic acid. The three diets, which differed only in fatty acid composition, were fed in random order for four weeks each. It was observed that although both of the polyunsaturated fat diets reduced the plasma cholesterol levels, only the salmon oil diet caused a significant decrease in triglyceride levels. Harris et al. [36] inferred that fatty acids present in fish oils are potentially useful in the control of both hypertriglyceridemia and hypercholesterolemia.

Subsequently, Harris et al. [37] also studied the effect of dietary fish oils on the plasma triglyceride and VLDL levels that occur physiologically after the induction of a high-carbohydrate diet. A baseline diet (45 percent fat, 10 percent protein, 45 percent carbohydrate) and two high-carbohydrate diets (15 percent fat, 10 percent protein, 75 percent carbohydrate) were fed to seven mildly hypertriglyceridemic, but otherwise healthy volunteers (22–54 years of age). One carbohydrate diet served as the control and the other contained cod liver oil. The baseline and control dietary fats were a mixture of peanut oil and cocoa butter. It was found that dietary omega-3 fatty acids from fish oil rapidly and markedly reduced VLDL triglyceride levels even in the face of a high-carbohydrate diet. Harris et al. [37] hypothesized that fish oil lowered plasma triglyceride levels by inhibiting the synthesis of VLDL triglyceride or by enhancing its clearance in the periphery. Cartwright et al. [41] inferred that modification of blood rheology by dietary omega-3 fatty acids is of potential value in the treatment of vascular disease.

STUDIES ON THE JAPANESE POPULATION

Apart from the Eskimo population, the changing patterns of ischemic heart disease, nutrient intake, and HDL cholesterol levels have been studied only among the Japanese [43,44,45,46,47,48,49]. The Japanese life style can be categorized into three types:

a. Farmland type, where the traditional life style dictates a diet consisting mainly of rice
b. Fishing village type, where the residents eat chiefly fish
c. Urban residents with a diet pattern similar to that of the Western world [43]

Hirai et al. [48] compared the dietary fatty acid composition and distribution of fatty acids in total plasma lipid of the residents of a fishing village and a farming village in the Chiba prefecture of Japan. The observations revealed:

1. Those living in the fishing village consumed 250 g of fish per person per day (equivalent to 2.5 g of EPA) and the farming village population ingested 90 g of fish per person per day (equivalent to 0.9 g of EPA).
2. The residents of the fishing village had a higher concentration of EPA and DHA in their blood plasma after 12 hours of fasting than those living in the farming village.

Another study conducted by the same research group [49] showed that the mean blood viscosity of the residents in the fishing village was significantly lower than that of those living in the farming village. These researchers [48,49] therefore inferred:

a. A seafood diet reduces blood viscosity, and EPA is mainly responsible for this effect.
b. Since increased blood viscosity is important in the etiology of thrombotic disorders, ingestion of seafood rich in EPA is beneficial to health.

The daily total lipid intake among the Japanese is about one-third of that of Americans, and the composition of the fatty acids in the diet and human adipose tissue is also quite different in the two countries. Though the amount of polyunsaturated fatty acids consumed is equal in the two countries, their chemical nature is different. Japanese consume large quantities of long-chain, highly polyunsaturated fatty acids (AA, EPA, and DHA) supplied from fish [44]. Over the last 30 years, it has also been deduced that the fat intake per person per day among Japanese has tripled. In 1950, the fat intake was 18 g per capita per day, and in 1975 it had increased to 52 g per capita per day. While, in 1950, for an average Japanese, fats constituted 7.7 percent of the total caloric intake, this percentage had increased to 21.4 percent by 1975. Up to 1970, animal and vegetable fat intake increased in parallel, and, by 1975, animal fat intake slightly exceeded that of vegetable fat. Although ischemic heart disease has increased about fourfold, it is not yet as prominent as stroke [43,46]; compared with other countries, the mortality from ischemic heart disease has remained low among Japanese. Blood lipid concentration, one of the major risk factors for ischemic heart disease, has also been reported as low [47].

Though the beneficial effect of consuming EPA through a high fish diet has been confirmed in Caucasian populations in short-term feeding studies [31,32,33,36,37,39], only among the Eskimos and Japanese do scientifically based inferences on the long-term beneficial effect of consuming EPA seem possible at present. In a study on aged persons (73.9 ± 7.8 years old) living on Kohama Island at Okinawa, Kagawa et al. [45] found:

1. The total amount of EPA in the serum of persons on Kohama Island (46.77 ± 7.46 mg/100 ml) was higher than that of people in Japan, owing to the higher intake of fresh fish (147.7 g/day).
2. A positive correlation existed between serum EPA concentration and HDL concentration.
3. A positive correlation existed among serum dihomo-gamma-linolenic acid (C20:3, omega-6) concentration and total cholesterol, triglyceride, and skin fold thickness.
4. The blood pressure level, incidence of abnormal ECG, and salt intake (6.2–8.3

g/day), estimated from urinalysis, were all lower than the average figures for Japanese of similar ages.

To study the effect of oral administration of EPA-rich fish oil concentrate on platelet aggregation and the release and the metabolism of (1-^{14}C) arachidonic acid and (U)-^{14}C EPA by human platelets, Hirai et al. [50] fed eight healthy male volunteers 18 capsules of fish oil concentrate (EPA 1.4 g) per day for four weeks. The findings were: *(1)* plasma and platelet concentrations of EPA markedly increased, while those of arachidonic acid and docosahexaenoic acid did not change; *(2)* platelet aggregation induced by collagen and ADP was reduced. It was also inferred that the release of AA from platelet lipids might be affected by the change in EPA content in platelets. Studies reported by Kagawa et al. [45] and Hirai's group [48,49,50] revealed that, like the Eskimo population, the Japanese population also records low rate of thrombotic disorders, presumably due to their EPA-rich diet.

CONCLUSION

A number of recently published studies confirm the fact that, compared to a typical American diet, a diet high in omega-3 fatty acids significantly reduces plasma cholesterol and triglyceride levels, improves fat tolerance, prolongs bleeding times, reduces platelet counts, and decreases platelet adhesiveness [2,3]. Omega-3 fatty acids contained in fish oils appear to have two anti-atherogenic effects, a hypolipidemic action, and an anti-thrombotic action upon the platelets [51].

Recently, Dyerberg [52] critically commented on the inference of Kromhout et al. [1] regarding the existence of an inverse relationship between the incidence of coronary heart disease and a relatively low level of fish intake. One should also take note that Kromhout et al. [1] incorrectly mentioned in their paper that Eskimos consume 400 g fish per capita per day. As has been clarified by Bang and Dyerberg [53], on a daily basis Greenland Eskimos ingest approximately 400 g of meat from arctic mammals (seal and whale) and not fish. At present, the precise mechanism by which polyunsaturated omega-3 fatty acids, which are abundant in fish oils and in the meat of arctic mammals, exert their effects on platelet activity and VLDL biosynthesis is unclear [54]. Future research should concentrate on long-term intervention studies on humans to determine the cardiovascular effects of eating fish.

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